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DIABETES INSIPIDUS

CLINICAL OBSERVATIONS IN FORTY-TWO CASES

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It is now well known that the pituitary gland is involved in the production of polydipsia and polyuria, but the explanation for the various pathologic changes reported to produce this symptom complex was not forthcoming until fairly recently. Fisher, Ingram and Ranson [1] made such a complete review of the literature and so excellent a presentation of experimental data that little, if any, information can be added along these lines. However, because of the complexity of the problem, the more important steps which led to the explanation of diabetes insipidus are briefly reviewed. In addition, the important aspects of 42 cases of diabetes insipidus at the University Hospital are presented. It is not intended that other, multiple factors in water balance be belittled, although they are outside the scope of this paper.

HISTORICAL AND EXPERIMENTAL BACKGROUND

It was not until 1913 that von den Velden [2] and Farini,[3] working independently, showed that in human beings with diabetes insipidus extracts of the posterior lobe of the pituitary had an antidiuretic effect. Shortly thereafter, the view was gaining strength that diabetes insipidus was caused by a deficiency of the secretion of the antidiuretic principle of the posterior lobe of the pituitary, when Camus and Roussy [4] demonstrated that a basal lesion of the hypothalamus which did not directly damage the hypophysis could cause this disturbance. It was also noted that total hypophysectomy did not increase the exchange of fluid.[5] Thereafter there arose two schools of thought, one of which expressed the belief that diabetes insipidus was due to a lesion of the posterior lobe of the pituitary, and the other, that it was caused by a lesion of the hypothalamus. It was not until the experimental work of Fisher, Ingram, Ranson and associates [6] that these opposing views were reconciled. It has been shown that there exists a hypothalamicohypophysial system, with an included supraopticohypophysial tract, which operates as a functional unit and that injury to any part of this system causes diabetes insipidus.

By recalling the anatomic relations, one can obtain a better understanding of the problem. In man the pituitary body is connected with the base of the brain just below the third ventricle by the pituitary stalk, or infundibular stem. It has been shown in experimental animals that through this stem pass fibers from the supraoptic nuclei, in the anterior part of the hypothalamus, to innervate the posterior lobe of the pituitary. The cells of the infundibular stem, the median eminence and the posterior lobe of the pituitary are similar histologically, and these three parts constitute the neurohypophysis, or pars nervosa. As is readily seen, the supraopticohypophysial tract, containing fibers passing from the supraoptic nuclei to the pars nervosa, is superficial and may be easily damaged by pathologic conditions in the floor of the third ventricle, in the

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1: Fisher, C.; Ingram, W. R., and Ranson, S. W.: Diabetes Insipidus and the Neuro-Hormonal Control of Water Balance: A Contribution to the Structure and Function of the Hypothalamico-Hypophyseal System, Edwards Brothers, Inc., Ann Arbor, Mich., 1938.

2. von den Velden, R.: Die Nierenwirkung von Hypophysenextrakten beim Menschen, Berl. klin. Wchnschr. **50**:2083, 1913.

3. Farini, A.: Diabete insipido ed opoterapia ipifisaria, Gaz. d. osp. **34**:1135, 1913.

4. Camus, J., and Roussy, G.: Polyurie expérimentale par lésions de la base du cerveau: La polyurie dite hypophysaire, Compt. rend. Soc. de biol. **75**:628, 1913; Polyurie par lésion de la région opto-pédonculaire de la base du cerveau: Mécanisme régulateur de la teneur en eau de l'organisme, ibid. **76**:773, 1914.

5. (*a*) Camus, J., and Roussy, G.: Hypophysectomie et polyurie expérimentales, Compt. rend. Soc. de biol. **75**:483, 1913. (*b*) Crowe, S. J.; Cushing, H., and Homans, J.: Experimental Hypophysectomy, Bull. Johns Hopkins Hosp. **21**:127 (May) 1910.

6. (*a*) Fisher, Ingram and Ranson,[1] (*b*) Fisher, C.; Ingram, W. R.; Hare, W. K., and Ranson, S. W.: The Degeneration of the Supraopticohypophyseal System in Diabetes Insipidus, Anat. Rec. **63**:29 (Aug. 25) 1935. (*c*) Magoun, H. W., and Ranson, S. W.: Role of Supra-Opticohypophysial Tract and Neurohypophysis in the Regulation of Water Exchange in the Monkey, Tr. Am. Neurol. A. **65**:63, 1939. (*d*) Fisher, C.: Diabetes Insipidus and Neurohormonal Control of Water Balance, Proc. Inst. Med. Chicago **13**:117 (May 15) 1940.

meninges at the base of the brain, in the anterior portion of the hypothalamus near the supraoptic nuclei, and within the pituitary stalk and the posterior lobe of the pituitary. Since secretion of the antidiuretic principle by the pars nervosa is dependent on innervation through this tract, the supraopticohypophysial tract is a functional unit, and injury anywhere along this tract may result in diabetes insipidus. Thus, the two schools of thought before mentioned, the hypophysists and the hypothalamists, had each a correct, but incomplete, explanation of the cause of diabetes insipidus. It has been definitely shown that the supraopticohypophysial tract must be injured bilaterally before diabetes insipidus results.[7]

ROLE OF THE PARS ANTERIOR

Not only the pars nervosa but the pars anterior has a function in water balance. While the pars nervosa has a known antidiuretic effect, the pars anterior has a diuretic effect. The pars anterior and the pars nervosa, however, are normally in equilibrium. Diabetes insipidus may be considered the result of an uncompensated activity of the pars anterior, unchecked by the antidiuretic factor of the pars nervosa.[8]

Although it is generally agreed that the pars anterior has a diuretic effect, there is a difference of opinion concerning the explanation of this action. Crowe, Cushing and Homans,[5b] in 1909, found that diabetes insipidus did not develop in totally hypophysectomized dogs. However, when the pars anterior was transplanted in these same dogs, polydipsia and polyuria developed. These symptoms disappeared when the transplant was removed. Von Hann[9] concluded that the pars anterior must be at least partially intact if destruction of the posterior lobe is to result in diabetes insipidus. He expressed the belief that this was perhaps the consequence of the secretion of a diuretic principle by the anterior lobe of the pituitary, which was antagonistic to the antidiuretic principle of the posterior lobe. Gersh[10] listed three possible ways in which the anterior lobe of the pituitary may have a diuretic effect: (1) by maintenance of general metabolism and activity at such a level that water exchange is kept at normal levels; (2) by the more specific thyrotropic factor, which stimulates the thyroid and thus influences metabolism and water exchange, and (3) by a specific diuretic principle, which is not the thyrotropic principle but which is ineffective in the absence of the secretion of the thyroid, being synergistic with the thyroid. Heinbecker and White[8] offered support of the third view. Numerous experiments have demonstrated the role played by the thyroid in maintaining a diuretic effect in animals with diabetes insipidus.[11] Fisher, Ingram and Ranson[1] concluded that the diuretic action of the pars anterior is not mediated through the thyroid gland alone. Although a syndrome simulating diabetes insipidus was produced in dogs and in man by administration of desoxycorticosterone acetate,[12] it was also concluded that the influence of the anterior lobe of the pituitary in maintaining maximal diabetes insipidus is not mediated through the adrenal cortex.[13]

ROLE OF THE PARS NERVOSA

The antidiuretic role of the pars nervosa is somewhat better understood. The evidence is well in favor of the hormonal nature of the antidiuretic substance. Compére[14] and Brull[15] anastomosed the carotid artery-jugular vein circulation of dogs having diabetes insipidus with the kidneys of normal dogs and thereby produced polyuria in the normal dogs. In the same experiment and under identical conditions,

7. Fisher, Ingram and Ranson.[1] Magoun and Ranson.[6c] Heinbecker, P., and White, H. L.: Hypothalamicohypophyseal System and Its Relation to Water Balance in the Dog, Am. J. Physiol. **133**:582 (July) 1941.

8. Heinbecker, P., and White, H. L.: The Role of the Pituitary Gland in Water Balance, Ann. Surg. **110**:1037 (Dec.) 1939.

9. von Hann, F.: Ueber die Bedeutung der Hypophysenveränderungen bei Diabetes insipidus, Frankfurt. Ztschr. f. Path. **21**:337, 1918.

10. Gersh, I.: Water Metabolism: Endocrine Factors, A. Research Nerv. & Ment. Dis., Proc. (1939) **20**:436, 1940.

11. Barnes, B. O.; Regan, J. F., and Bueno, J. G.: Is There a Specific Diuretic Hormone in the Anterior Pituitary? Am. J. Physiol. **105**:559 (Sept.) 1933. Biasotti, A.: Thyroïde et action diurétique de l'extrait anté-hypophysaire, Compt. rend. Soc. de biol. **115**:329, 1934. Biggart, J. H., and Alexander, G. L.: Experimental Diabetes Insipidus, J. Path. & Bact. **48**:405 (March) 1939. Mahoney, W., and Sheehan, D.: The Effect of Total Thyroidectomy upon Experimental Diabetes Insipidus in Dogs, Am. J. Physiol. **112**:250 (June) 1935.

12. Mulinos, M. G.; Spingarn, C. L., and Lojkin, M. E.: A Diabetes Insipidus-Like Condition Produced by Small Doses of Desoxycorticosterone Acetate in Dogs, Am. J. Physiol. **135**:102 (Dec.) 1941. Moehlig, R. C., and Jaffe, L.: Syndrome Simulating Diabetes Insipidus in Dogs Induced by Desoxycorticosterone Acetate: Clinical Observation of Syndrome with Addition of Tetany, J. Lab. & Clin. Med. **27**:1009 (May) 1942.

13. Schweizer, M.; Gaunt, R.; Zinken, N., and Nelson, W. O.: The Role of the Adrenal Cortex and the Anterior Pituitary in Diabetes Insipidus, Am. J. Physiol. **132**:141 (Feb.) 1941.

14. Compére, A.: Mécanisme de la polyurie hypophysaire, Arch. internat. de physiol. **36**:54 (Jan.) 1933.

15. Brull, L.: Transmission sanguine de la polyurie hypophysaire, Presse méd. **41**:1267 (Aug. 12) 1933.

however, perfusion of the kidneys of a normal dog with blood from a normal dog, without diabetes insipidus, did not result in polyuria. Various investigators, the first of whom were Houssay and Carulla,[16] showed that denervation of the kidneys did not prevent the usual course of experimentally induced diabetes insipidus. Furthermore, an antidiuretic substance was isolated from the urine of normal animals but not from animals with diabetes insipidus.[17] Recent observations by Haterius [18] supported the concept of the hormonal nature of the antidiuretic principle of the pituitary and verified the hypothesis that, under certain conditions at least, the release of the substance is under reflex control. It was found to be present in greater amounts in the urine of dehydrated animals than in normal, hydrated animals, apparently appearing when necessary to assist in retention of water during dehydration.[19] This substance is physiologically and chemically similar to solution of posterior pituitary. Heller [20] found that the antidiuretic principle at a p_H of from 0.57 to 10.0 is more stable than the other two substances of the posterior lobe of the pituitary, the oxytocic and the pressor. Assays for these substances from the neurohypophysis of normal cats and of cats with diabetes insipidus showed that they were absent or greatly diminished in cats with diabetes insipidus.[1]

The evidence indicates that the antidiuretic principle acts directly on the renal tubules, with stimulation of these cells to reabsorb more water from the lumen of the tubule, an action which leads to retention of body water and reduction in the flow of urine.[21] Therefore, in the absence of this principle in diabetes insipidus the polyuria is primary to the polydipsia. This is shown by the fact that cats with diabetes insipidus when deprived of fluid suffer rather rapid depletion of body fluid because they continue to excrete a great excess of water in the urine. When water can no longer be mobilized from extravascular sources the cats die, with physical symptoms resembling those of adrenal insufficiency.[22] The inability to concentrate urine is characteristic of patients with diabetes insipidus.

According to White and Findley [23] in patients with diabetes insipidus the renal tubules showed decreased sensitivity to acute changes in the amount of water or the concentration of salt in the blood. They also found that the chloride level of the serum fluctuated more in patients with diabetes insipidus than in normal persons. Curtis [24] observed that experimental diabetes insipidus in the dog was much less severe if the animal fasted and that the severity of the diabetes insipidus was roughly proportional to the amount of sodium chloride ingested. Swann and other observers [25] noted the immense increase in diuresis in animals with diabetes insipidus following increased intake of salt. There is good evidence, however, that diabetes insipidus is not chiefly a disturbance in sodium chloride metabolism.[25a] Winter and his associates [26] stated:

> Salt excretion is much less affected by pitressin in diabetes insipidus animals than in normals, although water excretion is more markedly affected in the for-

16. Houssay, B. A., and Carulla, J. E.: Polyurie par piqûre centrale chez les chiens â reins énervés, Compt. rend. Soc. de biol. **83**:1252, 1920.

17. Gilman, A., and Goodman, L. S.: The Secretion of an Antidiuretic Hypophyseal Hormone in Response to the Need for Renal Water Conservation, Science **84**:24 (July 3) 1936; The Secretory Response of the Posterior Pituitary to the Need for Water Conservation, J. Physiol. **90**:113 (July 15) 1937. Hare, K.; Hickey, R. C., and Hare, R. S.: The Renal Excretion of an Antidiuretic Substance by the Dog, Am. J. Physiol. **134**:240 (Sept.) 1941.

18. Haterius, H. O.: Evidence of Pituitary Involvement in the Experimental Control of Water Diuresis, Am. J. Physiol. **128**:506 (Feb.) 1940.

19. Gersh.[10] Footnote 17.

20. Heller, H.: The Effect of the Hydrogen-Ion Concentration on the Stability of the Antidiuretic and Vasopressor Activities of Posterior Pituitary Extracts, J. Physiol. **96**:337 (Aug. 14) 1939.

21. Fisher, Ingram and Ranson.[1] Gersh.[10] Shannon, J. A.: The Control of the Renal Excretion of Water: I. The Effect of Variations in the State of Hydration on Water Excretion in Dogs with Diabetes Insipidus, J. Exper. Med. **76**:371 (Oct.) 1942.

22. Fisher, Ingram and Ranson.[1] Hare, K.: Water Metabolism: Neurogenic Factors, A. Research Nerv. & Ment. Dis., Proc. (1939) **20**:416, 1940. Winter, C. A.; Ingram, W. R., and Gross, E. G.: Effect of Pitressin Injections upon the Serum Electrolytes and Water Exchange of Cats with Diabetes Insipidus and Adrenal Insufficiency, Am. J. Physiol. **127**:64 (Aug.) 1939.

23. White, H. L., and Findley, T., Jr.: Responses of Normal Subjects and of Patients with Diabetes Insipidus to Water and Salt Ingestion, J. Clin. Investigation **18**:377 (July) 1939.

24. Curtis, G. M.: The Production of Experimental Diabetes Insipidus, Arch. Int. Med. **34**:801 (Dec.) 1924.

25. Swann, H. G.: Recovery in the Rat from the Diabetes Insipidus Caused by Posthypophysectomy, Proc. Soc. Exper. Biol. & Med. **39**:255 (Nov.) 1938; Sodium Chloride and Diabetes Insipidus, Am. J. Physiol. **126**:341 (June) 1939. Swann, H. G., and Penner, B. J.: The Effect of Salts on the Diabetes Insipidus Following Posthypophysectomy in the Rat, Endocrinology **24**:253 (Feb.) 1939. Bellows, R. T.: Studies in Water Metabolism in Relation to the Nervous System, New York State J. Med. **39**:1470 (Aug. 1) 1939.

25a. Winter, C. A.; Sattler, D. G., and Ingram, W. R.: The Relationship Between Salt Intake and the Polyuria of Experimental Diabetes Insipidus, Am. J. Physiol. **131**:363 (Dec.) 1940.

26. Winter, C. A.; Ingram, W. R.; Gross, E. G., and Sattler, D. G.: Sodium and Chloride Balance in Cats as Affected by Diabetes Insipidus, Endocrinology **28**: 535 (April) 1941.

mer; it is concluded that the effects of pitressin on urine volume and on salt excretion are two independent mechanisms.

ROLE OF PITUITARY GLAND IN WATER BALANCE IN ABNORMAL CONDITIONS OTHER THAN DIABETES INSIPIDUS

Diabetes insipidus is not the only disease in which the pituitary plays a role in water balance. As has already been mentioned, in cases of simple dehydration the antidiuretic principle appears in the urine in greater amounts than under normal conditions, apparently as an overflow into the urine of an increased amount of the substance in the blood in order to conserve body fluid under such circumstances.[10] In cases of Simmonds' disease (hypopituitary cachexia), owing to deficiency of the secretion of the anterior lobe of the pituitary, both the intake and the output of fluid may sometimes be decreased to as low as 200 to 300 cc. per day,[27] probably as the result of diminution in the diuretic effect of the anterior lobe of the pituitary. In cases of Simmonds's disease there is also frequently atrophy of the adrenal cortex, presumably secondary to withdrawal of the adrenotropic principle of the anterior lobe of the pituitary, with resultant changes in metabolism of sodium chloride and fluid similar to those in cases of Addison's disease.[28] It has been suggested that the polyuria sometimes associated with Cushing's syndrome (basophilic adenoma) may possibly be due to hyperactivity of the anterior lobe of the pituitary rather than to pressure on and associated diminished function of the posterior lobe.[29] However, the hyperfunction of the adrenal cortex usually present in cases of Cushing's sylndrome also has some effect on exchange of fluids, and, as mentioned previously, desoxycorticosterone acetate has produced a syndrome simulating diabetes insipidus.[12]

From the urine of patients with eclampsia Teel and Reid[30] recovered in large amounts antidiuretic substance similar to solution of posterior pituitary. They also observed that persons with eclampsia are sensitive to solution of posterior pituitary injected hypodermically in small amounts, whereas a normally pregnant woman does not show this pronounced sensitivity and has little, or no, antidiuretic substance in her urine. Eclampsia is possibly due to oversecretion of the posterior lobe of the pituitary, with its resultant antidiuretic, pressor and oxytocic effects. The edema may be due to retention of fluid as a result of an increase in the antidiuretic principle. In frogs, as well as in some mammals, water intoxication has been produced by administration of large amounts of water and posterior pituitary solution,[31] possibly on the same physiologic basis as that of retention of fluids associated with eclampsia.

It has been shown that estrogen in large doses can depress the activity of the anterior lobe of the pituitary, including its diuretic function. Thus, so-called menstrual edema appears at the phases of the human menstrual cycle which coincide with the diminished diuretic effect of the anterior lobe of the pituitary, with resultant retention of fluid.[29] The edema which appears with the maximal secretion of estrogen, however, may be caused by retention of sodium chloride produced by the estrogen.[32]

The pituitary gland as "master regulator" of hormonal secretion most likely plays a role in water metabolism not only through its control of the thyroid, the adrenals and the gonads, but through its effect on the pancreas, and possibly in other ways.

CASES OF DIABETES INSIPIDUS STUDIED AT THE UNIVERSITY HOSPITAL

With the previously mentioned facts in mind, the records of all cases with the diagnosis of diabetes insipidus at the University Hospital were studied. In order to have a definite idea as to which cases should be included in the study,

27. (*a*) Silver, S.: Simmonds' Disease (Cachexia Hypophyseopriva): Report of a Case with Postmortem Observations and a Review of the Literature, Arch. Int. Med. **51**:175 (Feb.) 1933. (*b*) Gunther, L., and Courville, C. B.: Hypophyseal Cachexia (Simmonds' Disease) with Atrophy of the Anterior Lobe of the Pituitary Gland, J. Nerv. & Ment. Dis. **82**:40 (July) 1935. (*c*) Fisher, Ingram and Ranson.[1]

28. Stephens, D. J.: Chloride Excretion in Hypopituitarism with Reference to Adrenocortical Function, Am. J. M. Sc. **199**:67 (Jan.) 1940.

29. Shapiro, B. G.: Control of Urinary Secretion by the Anterior Pituitary, Lancet **2**:1457 (Dec. 24) 1938.

30. Teel, H. M., and Reid, D. E.: Observations upon the Occurrence of an Antidiuretic Substance in the Urine of Patients with Pre-Eclampsia and Eclampsia, Endocrinology **24**:297 (March) 1939.

31. (*a*) Fisher, Ingram and Ranson.[1] (*b*) Boyd, E. M., and Young, F. M.: The Effect of a Wide Range of Doses of Pituitary (Posterior Lobe) Extract on the Brunn Reaction in Frogs, Quart. J. Pharm. & Pharmacol. **13**:64 (Jan.-March) 1940. (*c*) Boyd, E. M., and Mack, E. G.: A Method of Assaying Pituitary Water Retention Principle, Endocrinology **26**:153 (Jan.) 1940. (*d*) Boyd, E. M.; Clark, K. J., and Smith, A. E.: The Intake of Water by Frogs During Their Reaction to Pituitrin, Am. J. Physiol. **129**:645 (June) 1940. (*e*) Thorn, G. W., and Stein, K. E.: Pitressin Tannate Therapy in Diabetes Insipidus, J. Clin. Endocrinol. **1**:680 (Aug.) 1941.

32. Thorn, G. W.; Nelson, K. R., and Thorn, D. W.: A Study of the Mechanism of Edema Associated with Menstruation, Endocrinology **22**:155 (Feb.) 1938. Thorn, G. W., and Engel, L. L.: The Effect of Sex Hormones on the Renal Excretion of Electrolytes, J. Exper. Med. **68**:299 (Sept.) 1938.

arbitrary criteria were established. Only cases were included in which there were a daily intake of fluid of at least 6,000 cc. and a daily output of urine of at least 4,000 cc., with the specific gravity of the urine at no time exceeding 1.008. In the cases of children, corresponding increases in intake and output of fluid for the age and weight of the child were used as standards. It is known that some objections to these specific criteria may be found. As Magoun and Ranson showed, there is a physiologic reserve of the pars nervosa comparable to that of other parts of the body. Well over half of the pars nervosa bilaterally must be nonfunctioning before even the slightest increase in exchange of fluids occurs.[7] With differences in the amount of the nonfunctioning portion, there may be all degrees of diabetes insipidus, varying from the slightest evidence to a great increase in exchange of fluid. Thus, some cases of mild diabetes insipidus may have been omitted on the basis of these criteria. Moreover, all the patients did not have renal concentration tests. It is possible, then, that with the standards as established a few cases of psychogenic polydipsia and polyuria may have been included in this report. The criteria were established, however, in order to specify exactly what cases were considered.

Between January 1926 and January 1943, 42 cases with a typical history of diabetes insipidus, aglycosuria and fulfilment of the preceding criteria were studied at the University Hospital. In each case considered the daily intake of fluid and the daily output of urine were recorded, with repeated determinations of the specific gravity of the urine. In addition, in nearly all cases roentgenograms of the skull were taken, and careful neurologic and ophthalmoscopic tests, as well as routine physical examinations, were made. Unfortunately, the records revealed that renal concentration tests were made in only 6 cases.

An adequate postmortem examination was performed in only 2 cases.[33] In 1 of these (case 1) there was generalized carcinomatosis, with diffuse carcinomatous replacement of the posterior lobe of the pituitary and involvement of a small amount of the anterior lobe. In the other (case 2) a medulloblastoma involved the hypothalamus, the third ventricle and the posterior lobe of the pituitary, with little implication of the anterior lobe. The pathologic observations in each case substantiated the results of previously mentioned experimental work on the anatomic changes which result in diabetes insipidus. The supraopticohypophysial tract had been destroyed, a normally functioning pars anterior remaining in each case.

An attempt was made to determine the cause of the diabetes insipidus and to evaluate the response to various forms of therapy tried in the cases reported. In the cases studied the response to preparations of posterior pituitary, administered by four methods, was considered: Solution of posterior pituitary U. S. P. or pitressin was injected hypodermically; pitressin was administered intranasally in the form of a liquid or a jelly, and pitressin tannate in oil was injected intramuscularly. In the cases in which solution of posterior pituitary was given hypodermically, an average daily dose of 2 to 2.5 cc. was divided into two to four daily injections. Occasional patients received as much as 3 cc. of solution of posterior pituitary or of pitressin daily. Pitressin administered intranasally as a liquid or as a jelly [33a] was given in corresponding amounts daily, in divided doses. Pitressin tannate in oil was given in only 4 cases (9, 17, 41 and 42). The amount and frequency of injection are mentioned in the summary of each case. A "good" therapeutic response in these cases was a diminution in the daily intake and output of fluids to less than one-third the amount prior to administration of posterior pituitary, or a diminution in the intake of fluid to within the normal range of 3,000 cc. or less daily for an adult, or corresponding amounts for children. A "moderate" therapeutic response was a diminution in the daily exchange of fluids to less than two-thirds that prior to administration of posterior pituitary. A "poor" response indicated less improvement than this, or none at all.

The data in the cases are summarized in table 1. In the following section the cases are briefly summarized and classified according to the etiologic factors involved.

REPORT OF CASES

Tumors Involving the Pituitary Gland (cases 1 to 11).—In these 11 cases there was clinical and roentgenographic evidence of tumor involving the pituitary gland. They included the 2 cases with postmortem verification mentioned previously (cases 1 and 2). In case 1, roentgen irradiation of the hypothalamic and pituitary regions failed to relieve the patient of the symptoms of diabetes insipidus. In case 3, eight months after the onset of symptoms of diabetes insipidus, a tumor appeared on the upper thoracic portion of the spine, biopsy of which revealed a round cell sarcoma, resembling Ewing's tumor (angioendothelioma). Thus, diabetes insipidus was the first symptom of sarcoma in this case. In case 4, first seen in 1926, no other evidence of a malignant growth appeared elsewhere

33. The pathologic observations reported in this paper are from the records of the Department of Pathology, University of Michigan.

33a. The pitressin jelly used consisted of a water-soluble gum, such as tragacanth, containing pitressin in a concentration of 10 pressor units to each gram.

TABLE 1.—*Summary of Data on Diagnostic Criteria, Etiologic Factors and Therapeutic Responses in Forty-Two Cases of Diabetes Insipidus Considered in This Report*

Case No.	Age (Years) When Patient Was First Seen	Duration of Condition Prior to Admission to Hospital	Daily Fluid Intake, Cc.	Daily Output of Urine, Cc.	Specific Gravity of Urine	Etiologic Factors and Associated Diagnoses	Response to Preparations of Posterior Pituitary: Hypodermic Injection of Solution of Posterior Pituitary	Response to Preparations of Posterior Pituitary: Intranasal Application: Solution	Response to Preparations of Posterior Pituitary: Intranasal Application: Jelly	Comment
1	45	6 mo.	6,000 to 10,000	4,000 to 8,000	1.004 to 1.008	Generalized carcinomatosis, with diffuse carcinomatous replacement of posterior lobe and small amount of anterior lobe	Good	.....	.....	Poor results in control of diabetes insipidus after roentgen therapy to regions of hypothalamus and posterior lobe of pituitary; postmortem examination
2	29	7 mo.	8,000 to 15,000	5,000 to 18,000	1.001 to 1.007	Medulloblastoma, involving hypothalamus, third ventricle and posterior lobe of pituitary, with little involvement of anterior lobe	Good	.....	Poor	Postmortem examination
3	8	4 mo.	7,000 to 10,000	5,000 to 8,000	1.000 to 1.006	Round cell sarcoma; Ewing's tumor involving spine and skull	Good	.....	Poor	Biopsy specimen from upper thoracic part of spine, where first evidence of tumor appeared 8 months after onset of diabetes insipidus
4	24	2 yr.	8,000 to 10,000	7,000 to 8,000	1.000 to 1.004	Round cell sarcoma, suggesting unpigmented melanotic sarcoma, with multiple osteolytic neoplastic lesions, including metastases to skull	Good	Moderate	.....	Biopsy specimen from vulva 6 years after onset of diabetes insipidus, which responded well to roentgen irradiation as did neoplastic lesions
5	2	6 wk.	6,000 to 8,000	4,000 to 5,000	1.000 to 1.006	Lymphosarcoma of large round cell type with multiple metastases to scalp	Good	.....	.....	Biopsy specimen from behind right ear
6	13	6 yr.	8,000 to 12,000	6,000 to 9,000	1.001	Fibroma of right antrum with sarcomatous changes at age of 1 year, with curettage and roentgen irradiation of antrum	.....	.....	.....	Patient drank own urine when an attempt was made to limit intake of fluid to 2 liters per day
						On admission, clinical evidence of hypopituitarism and hypothyroidism; basal metabolic rate —17%				Thyroid 0.065 Gm. daily, decreased, rather than increased, exchange of fluid
7	59	6 wk.	7,000 to 9,000	5,000 to 7,000	1.008	Mastectomy for carcinoma of breast 8 months prior to admission; local recurrence, with metastases to regional lymph nodes, biopsy of node showing adenocarcinoma, compatible with origin in breast	Poor, but trial inadequate	.....	.....	Onset of headache with diabetes insipidus; diabetes insipidus relieved by roentgen irradiation (cross firing) of brain, including pituitary and hypothalamic regions
8	15	1 yr.	4,000 to 7,000	3,000 to 5,000	1.004 to 1.006	Cystic adamantinoma with suprasellar tumor of pituitary body removed by osteoplastic craniotomy, at which time pituitary stalk was cut	Good	.....	.....	No change in diabetes insipidus after operation
9	12	1 yr.	4,000 to 6,000	3,000 to 5,000 (?) (patient incontinent)	1.002 to 1.005	Calcified suprasellar and intrasellar cystic adamantinoma removed by osteoplastic craniotomy; clinical symptoms of decreased pituitary and thyroid function; basal metabolic rate —30 %	.....	.....	.....	Specific gravity of urine 1.008 in 14 hour urine concentration test; pitressin tannate in oil, 1 cc. every 3 days intramuscularly, good therapeutic results, with specific gravity reaching 1.024
10	4	1 yr.	2,500 to 3,500	1,500 to 2,000	1.003	Cystic adamantinoma with suprasellar and intrasellar cysts, removed by osteoplastic craniotomy	.....	.....	.....	Slight improvement in diabetes insipidus several years after operation
11	3	0	2,500 to 3,000	1,500 to 2,000	1.000 to 1.005	Onset 6 days after removal of cystic adamantinoma of pituitary, at which time pituitary stalk was cut	.....	.....	.....	Diabetes insipidus of 6 months' duration after operation, condition then subsiding
12	26	6 wk.	12,000 to 30,000	12,000 to 22,000	1.000 to 1.006	Clinical evidence of glioma of diencephalon (?)	Good	.....	.....	Good response of diabetes insipidus to roentgen irradiation of pituitary and hypothalamic regions
13	7	2 mo.	1,500 to 3,000	1,000 to 2,000	1.005 to 1.008	Tumor in midline, involving hypothalamus but not pituitary, as observed in exploratory craniotomy	.....	.....	.....	Postoperative death without postmortem examination
14	3	2 yr.	2,000 to 5,000	1,000 to 4,000	1.002 to 1.006	Hand-Schüller-Christian disease (xanthamatosis)	.....	.....	.....	
15	5	?	2,500 to 5,000	1,750 to 4,500	1.003 to 1.006	Hand-Schüller-Christian disease (xanthomatosis)	.....	.....	.....	Good response to diabetes insipidus to roentgen irradiation of pituitary region
16	3	6 mo.	4,000 to 8,000	4,000 to 8,000	1.004 to 1.008	Hand-Schüller-Christian disease (xanthomatosis)	.....	.....	.....	Moderate response of diabetes insipidus to roentgen irradiation of skull
17	2	1 mo.	6,000 to	3,000 to	1.000	Radical mastoidectomy (right) and craniec-	Good			

16	3	6 mo.	4,000 to 8,000	4,000 to 8,000	1.004 to 1.008	Hand-Schüller-Christian disease (xanthomatosis)	.....	.....	.....	Moderate response of diabetes insipidus to roentgen irradiation of skull
17	2	1 mo.	6,000 to 9,000	3,000 to 8,000	1.000	Radical mastoidectomy (right) and craniectomy of greater part of right temporal bone 1 year before; pathologic diagnosis then "lymphosarcoma"; observations and biopsy of lymph nodes on admission indicated Hand-Schüller-Christian disease (xanthomatosis)	Good	.....	.....	Pitressin tannate in oil, 0.5 cc. every 2 days, given intramuscularly insufficient, but 0.5 cc. given daily gave good results, with specific gravity of urine reaching 1.018-1.022; roentgen irradiation of middle cranial fossa
18	22	10 yr.	11,000 to 13,000	6,000 to 11,500	1.003 to 1.006	Chronic encephalitis with parkinsonism	Good	Good	Moderate	
19	33	3 yr.	7,000 to 8,000	5,000 to 6,000	1.006	Chronic encephalitis with parkinsonism	.....	.....	.....	
20	36	3 yr.	5,000 to 10,000	7,000 to 9,000	1.004 to 1.007	Chronic encephalitis with parkinsonism	.....	.....	.....	
21	21	6 yr.	7,000 to 11,000	4,000 to 11,000	1.002 to 1.004	Chronic encephalitis with parkinsonism	.....	Good	.....	Low salt diet beneficial in lowering intake and output of fluid
22	18	2 yr.	6,500 to 11,000	4,000 to 7,500	1.001 to 1.008	Chronic encephalitis	.....	Good	.....	
23	33	10 mo.	8,000 to 15,000	7,000 to 10,000	1.002 to 1.005	Meningitis of unknown origin and encephalitis	Moderate	.....	Moderate	
24	42	1 yr.	6,000 to 10,000	4,000 to 8,000	1.001 to 1.003	Chronic encephalitis and narcolepsy (?)	Good	Good	.....	Considerable nasal irritation following intranasal administration of solution of posterior pituitary
25	38	1 yr.	6,000 to 8,000	5,000 to 7,000	1.001 to 1.006	Syphilis of central nervous system	.....	.....	.....	Disappearance of diabetes insipidus with satisfactory antisyphilitic therapy
26	34	1 yr.	5,000 to 9,000	4,000 to 7,000	1.001 to 1.008	Syphilis of central nervous system	Good	.....	.....	Disappearance of diabetes insipidus with satisfactory antisyphilitic therapy; 18 hour urine concentration test showed specific gravity 1.008 without posterior pituitary and 1.019 with posterior pituitary
27	52	2 yr.	7,000 to 10,000	5,000 to 7,000	1.002 to 1.006	Syphilis	Good	.....	.....	
28	6	2 yr.	3,000 to 5,000	2,500 to 6,500	1.003 to 1.005	Post-traumatic injury to head	Good	.....	Poor	Onset immediately after blow on head
29	30	15 yr.	10,000 to 15,000	9,000 to 12,500	1.002 to 1.006	Post-traumatic injury to head	Good	Good	Poor	Onset immediately after blow on head
30	11	18 mo.	5,000 to 11,000	3,000 to 13,000	1.000 to 1.004	Post-traumatic injury to head (?)	.....	.....	.....	Onset about 6 months after blow on head
31	28	2½ yr.	10,000 to 12,000	8,000 to 11,000	1.002	Self-induced abortion, followed in 2 days by onset of diabetes insipidus; pituitary infarction (?)	Good	.....	Poor	
32	54	19 yr.	6,000 to 10,000 (?)	4,000 to 6,000 (?)	1.004	Cerebrovascular accident, with right hemiplegia and onset of diabetes insipidus at same time	.....	.....	.....	
33	49	20 days	5,500 to 6,800	4,000 to 6,000	1.000 to 1.001	Subarachnoid hemorrhage at onset of diabetes insipidus	.....	.....	.....	
34	23	1 yr.	19,000 to 35,000	16,000 to 32,000	1.000 to 1.003	Acute delirium, cause unknown; clinical evidence of hypothalamic damage	.....	.....	.....	Loss of weight 6 Kg. during 12 hour urine concentration test, with specific gravity reaching 1.003
35	26	2½ yr.	9,000 to 18,000	6,000 to 10,000	1.000 to 1.007	Conversion hysteria (?)	.....	.....	.....	Eighteen hour urine concentration test showed specific gravity of 1.007
36	8	Unknown	3,500 to 6,000	2,500 to 4,500	1.001 to 1.005	Early psychosis (?)	Good	.....	.....	
37	18	2½ yr.	7,000 to 9,000	5,000 to 6,000	1.003 to 1.005	?	Good	Good	.....	
38	42	1 yr.	16,000 to 18,000	12,000 to 16,000	1.000 to 1.002	?	Good	Good	.....	
39	11	5 yr.	5,000 to 9,000	4,500 to 9,000	1.001 to 1.006	?	Good	Poor	Poor	
40	4	5 mo.	2,500 to 6,000	1,600 to 5,900	1.000 to 1.008	?	Good	.....	.....	
41	2	4 mo.	3,500 to 5,500	2,200 to 3,500	1.000 to 1.003	?	Good	.....	.....	Pitressin tannate in oil, 0.5 cc. daily, gave excellent therapeutic results, with specific gravity of urine rising to 1.014-1.030 and with drop in output of urine to as low as 200-500 cc. daily
42	44	3 mo.	7,000 to 10,000	5,000 to 8,000	1.001 to 1.006	Onset of diabetes insipidus at onset of menopause; protein of spinal fluid elevated to 70 mg. per 100 cc.; abnormal electroencephalogram	.....	.....	Poor	Pitressin tannate in oil, 1 cc. every 2 days, gave good therapeutic results, with specific gravity of urine increasing to 1.023-1.025; loss of weight 3 Kg. in 24 hours on limited intake of fluid

until six years after the onset of polydipsia and polyuria (1930), at which time a round cell sarcoma, suggesting an unpigmented melanotic sarcoma, was reported on the basis of biopsy of a lesion which had appeared on the vulva. There were then multiple osteolytic neoplastic lesions, including metastases throughout the skull, all of which responded well to roentgen therapy, with permanent cure of the diabetes insipidus. The patient was still alive in January 1941, at which time she had a squamous cell carcinoma of the vulva. Thus, in this case diabetes insipidus preceded the etiologic diagnosis of melanotic sarcoma by six years. In case 5 biopsy of a nodule behind the right ear revealed a lymphosarcoma of large round cell type, which involved the pituitary, as well as multiple other areas on the scalp. The patient described in case 6 was admitted to the University Hospital at the age of 1 year, six years prior to the onset of his diabetes insipidus; at that time a fibroma was present in the right antrum, curettage of which revealed sarcomatous changes, also involving bone. He received roentgen radiation over the antrum at the time. Twelve years later he returned, with diabetes insipidus and clinical evidence of decrease in function of the pituitary and the thyroid. His parents had observed that when they tried to limit his fluid intake to 2 liters daily, he drank his own urine. His basal metabolic rate was —17 per cent. When he was given 0.065 Gm. of thyroid daily, the intake of fluid and output of urine slightly decreased, and the basal metabolic rate increased to —10 per cent. Involvement of the pituitary was considered as probably due to extension of the sarcomatous changes previously observed, although this was not proved and there was little other evidence of sarcoma at the time. The diabetes insipidus in case 7 was obviously due to metastasis from the carcinoma of the breast, for which a mastectomy had been done six months prior to onset of the diabetes insipidus. There were other evidences of metastases, and biopsy of a specimen from a regional lymph node showed adenocarcinoma, compatible with the origin in the breast. Roentgen irradiation of the hypothalamic and pituitary regions relieved the patient of her polydipsia and polyuria. The diabetes insipidus in cases 8, 9 and 10 was caused by cystic adamantinoma involving the pituitary body and removed by osteoplastic craniotomy. Only in case 10 was there slight improvement in the diabetes insipidus several years after operation. In case 9 intramuscular injection of pitressin tannate in oil, 1 cc. every three days, gave good therapeutic results, the specific gravity of the urine being raised to 1.024, whereas it had previously been 1.008 in a fourteen hour renal concentration test. It is interesting that in this case, in spite of clinical symptoms of hypopituitarism and hypothyroidism and a basal metabolic rate of —30 per cent, symptoms of diabetes insipidus were pronounced. In spite of the cystic adamantinoma removed in case 11, the onset of the diabetes insipidus occurred six days after the pituitary stalk had been cut, evidence that the diabetes was a result of section of the stalk rather than of the tumor. The diabetes insipidus in this case subsided in six months.

Tumors Involving the Hypothalamus (cases 12 and 13).—There was clinical evidence of a tumor involving the hypothalamus in 2 cases. Although the presence of a tumor was not pathologically proved in case 12, there was a good response of the diabetes insipidus to roentgen irradiation over the pituitary and the hypothalamic region. In case 13 an exploratory craniotomy revealed a tumor in the midline which involved the hypothalamus, but not the pituitary. No specimen was taken for biopsy, and the patient died after operation. Autopsy was not performed.

Hand-Schüller-Christian Disease (Xanthomatosis) (cases 14 to 17).—In 4 cases of diabetes insipidus Hand-Schüller-Christian disease was present. The diabetes insipidus in case 15 responded well to roentgen irradiation of the pituitary region, and there was a moderate response to similar therapy in case 16. In case 17 radical mastoidectomy (right side) and craniectomy of the greater part of the right temporal bone were done at the University Hospital one year prior to the onset of the diabetes insipidus. Pathologic examination then revealed a lymphosarcoma. When the patient was admitted to the hospital one year later, the clinical observations and pathologic changes noted in biopsy of a lymph node were characteristic of Hand-Schüller-Christian disease. In this case, intramuscular injection of 0.5 cc. of pitressin tannate in oil every two days was insufficient to control the diabetes continuously, but administration of 0.5 cc. daily gave good therapeutic results, with an increase in the specific gravity of the urine from 1.000 prior to therapy to from 1.018 to 1.022 after therapy. This patient received roentgen therapy to the middle cranial fossa but has not yet returned for check-up observation.

Chronic Encephalitis (cases 18 to 24).—In 7 cases there was clinical evidence of chronic encephalitis. In 4 of these cases (18 to 21) there was associated parkinsonism. Case 18 has been reported in detail by Himler.[34] In case 21 a low salt diet was beneficial in lowering the intake and output of fluid, although administration of posterior pituitary solution was also necessary to control the symptoms. In case 23 there was clinical evidence of associated meningitis of undetermined cause, as well as encephalitis. In addition to encephalitis, the patient in case 24 had a condition which had been diagnosed as narcolepsy. Although this patient responded well to intranasal administration of a solution of pitressin, this substance produced considerable nasal irritation, and medication had to be changed to hypodermic injection of solution of posterior pituitary for control of symptoms.

Syphilis (cases 25 to 27).—Syphilis was present in 3 cases, although there was evidence of syphilis of the central nervous system only in cases 25 and 26. In both these cases the diabetes insipidus completely disappeared with satisfactory antisyphilitic therapy. Because the patient did not return for a check-up after treatment, this cannot be stated in regard to case 27. In case 26 the patient had an eighteen hour urine concentration test, with a specific gravity of 1.088, while not receiving solution of posterior pituitary. The same test repeated while the patient was receiving 1 cc. of the substance hypodermically twice a day resulted in a specific gravity of 1.019.

Post-Traumatic Injury to the Head (cases 28 to 30).—In cases 28 and 29 the polydipsia and polyuria were obviously post-traumatic in origin, the onset in each case immediately following a blow to the head which conceivably could have injured the pituitary stalk. The diabetes insipidus in case 30 may possibly have been of post-traumatic origin, although the symptoms did not appear until six months after a severe blow

34. Himler, L. E.: Diabetes Insipidus After Epidemic Encephalitis, J. Michigan State Med. Soc. **34**:350 (June) 1935.

to the head. No other cause for the diabetes insipidus could be determined in this case.

Pituitary Infarction (case 31 [?]).—The onset of the diabetes insipidus in case 31 was two days after a self-induced abortion. Although it seems unlikely, this condition could have been an embolic phenomenon or, more likely, the result of postabortal thrombosis of pituitary vessels, as has been reported[35]; or it may have been due to postmortem necrosis of the pituitary.[36]

Cerebrovascular Accident (case 32).—In case 32 the appearance of the diabetes insipidus was associated with the onset of hemiplegia on the right side, obviously due to a cerebrovascular accident.

Subarachnoid Hemorrhage (case 33).—In case 33 the onset of polyuria and polydipsia followed a proved subarachnoid hemorrhage, most likely originating near the supraopticohypophysial tract.

Acute Delirium, of Unknown Cause (case 34).—The onset of the diabetes insipidus in case 34 was associated with acute delirium of questionable origin. Thereafter, the patient had all the signs and symptoms one would expect in a person with irritation or damage to the hypothalamus, including a return to the lower levels of psychomotor activity, the patient easily becoming enraged and acting more like an animal than a human being. In February 1941, seven years after the patient was seen at the University Hospital, he still had polyuria and polydipsia and was uncontrollable, being an inmate in a state asylum. During a twelve hour renal concentration test this patient lost 6 Kg. in weight, and his urine had a specific gravity of 1.003. At one time his daily intake of fluid was recorded as 35,000 cc., with a daily output of urine of 32,000 cc. It was felt that this patient had organic involvement of the hypothalamus.

Undetermined Etiologic Factors (cases 35 to 42).—In 8 cases no cause whatever could be found for the diabetes insipidus. Although in case 35 there was clinical evidence of questionable conversion hysteria to account for the polyuria, polydipsia and associated symptoms, an eighteen hour renal concentration test revealed a specific gravity of only 1.007, a result indicating an organic cause of the diabetes. In case 36 an associated clinical diagnosis of "early psychosis" was established. In case 41 a good therapeutic response followed hypodermic injection of pitressin, but a better response was obtained to intramuscular injection of pitressin tannate in oil, 0.5 cc. daily, which lowered the output of urine to as little as 200 to 500 cc. daily, with the specific gravity rising to from 1.014 to 1.030. In case 42 the onset of diabetes insipidus occurred at the onset of the menopause. Although the etiologic factor was not determined, an electroencephalogram was abnormal, and the protein content of the spinal fluid was elevated to 70 mg. per hundred cubic centimeters. This patient lost 3 Kg. in weight during a twenty-four hour interval on a limited intake of fluid, during which time the specific gravity of the urine was 1.006. Intramuscular injection of pitressin tannate in oil, 1 cc. every other day, resulted in a good therapeutic response, the specific gravity of the urine increasing to from 1.023 to 1.025.

35. Simmonds, M., cited by Silver,[27a] Reye, cited by Silver.[27a]

36. Sheehan, H. L.: Simmonds' Disease Due to Post-Partum Necrosis of the Anterior Pituitary, Quart. J. Med. **32**:277 (Oct.) 1939.

ANALYSIS OF CASES

On the basis of these observations, it was concluded that there was rather definite evidence of involvement of the supraopticohypophysial tract and that a fairly certain etiologic diagnosis was established in cases 1 to 33 inclusive (table 2). It was further concluded that definite organic changes were present in the hypothalamus in case 34, although the cause was unknown. No etiologic diagnosis could be established in cases 35 to 42, although the low specific gravity noted in urine concentration tests in cases 35 and 42 indicated an organic basis for the polydipsia and polyuria. In the remaining 6 instances (cases 36 to 41) the condition may have been of psychogenic origin, since no urine concentration tests were performed, or the diagnosis of an organic etiologic factor may have been missed and will become apparent in the future.

TABLE 2.—*Causes of Diabetes Insipidus in Cases Considered in This Report*

Cause	No. of Cases	Percentage
Tumor of pituitary	11	26
Tumor of hypothalamus	2	5
Hand-Schüller-Christian disease	4	10
Chronic encephalitis	7	16.6
Syphilis	3	7
Post-traumatic injury to head	3	7
Pituitary infarction (?)	1	2.4
Cerebrovascular accident	1	2.4
Subarachnoid hemorrhage	1	2.4
Hypothalamic damage, cause unknown	1	2.4
Undetermined cause	8	19
Total	42	100

One of the striking features of the cases studied was the early age of onset of the diabetes insipidus. In this series of cases the average age at the time of onset of the polydipsia and polyuria was 21 years (table 3). In 17 of the 42 cases the onset was before the age of 10 years, and in only 2 instances (cases 7 and 27) was the onset at the age of 50 or later. The oldest patients in this series were those whose diabetes was due to syphilis, with onset at the average age of 40 years. In the cases in which the cause was malignant neoplasm (cases 1 to 7), the ages at onset varied from 2 to 59 years, with an

TABLE 3.—*Ages at Time of Onset of Diabetes Insipidus in Cases Considered in This Report*

Age Groups (Yr.)	No. of Cases	Percentage
0 to 10	17	40
10 to 20	6	14
20 to 30	7	17
30 to 40	5	12
40 to 50	5	12
Over 50	2	5
Total	42	100

Average age at onset, 21 years

average of 24 years. The average age of onset of diabetes insipidus due to Hand-Schüller-Christian disease (cases 14 to 17) was 2 years. As would be expected in a syndrome with so many different etiologic factors, there was no significant variation in sex incidence, 22 of the patients being females and 20 males.

In cases of diabetes insipidus with an etiologic factor amenable to specific therapy, treatment of the causative factor was tried. Of 4 cases (1, 4, 7 and 12) in which roentgen irradiation of the pituitary and hypothalamus was carried out because of neoplasm involving these regions, relief of the symptoms of diabetes insipidus was obtained in 3 (cases 4, 7 and 12). If roentgen irradiation of the pituitary region had been done in case 4 when the patient was first seen in the University Hospital, in 1926, the diabetes insipidus would probably have responded to this form of therapy then as well as it did in 1930, after the etiologic factor had been determined.

TABLE 4.—*Therapeutic Response of Diabetes Insipidus to Preparations of Posterior Pituitary in Cases Considered Here*

	Intramuscular Injection of Pitressin Tannate in Oil		Hypodermic Injection of Solution of Posterior Pituitary or Pitressin		Intranasal Application of Solution of Pitressin		Intranasal Application of Pitressin Jelly	
Therapeutic Response	No. Cases	Percentage	No. Cases	Percentage	No. Cases	Percentage	No. Cases	Percentage
Good	4	100	21	91	8	80	0	0
Moderate	0	0	1	4.5	1	10	2	22
Poor	0	0	1	4.5	1	10	7	78
Total	4	100	23	100	10	100	9	100

The neoplasm in case 1 was apparently not radiosensitive. Of the instances of cystic adamantinoma removed by osteoplastic craniotomy, only in case 10 was there slight relief of the diabetes insipidus several years after operation. Apparently, changes beyond repair had already occurred in the supraopticohypophysial tract in cases 8 and 9. Sufficient damage to the tract to produce diabetes insipidus had not occurred in case 11 before operation. Of the cases of Hand-Schüller-Christian disease (xanthomatosis) in which roentgen therapy was applied to the region of the pituitary, a good response was obtained in case 15 and a moderate response in case 16. In 2 cases of diabetes insipidus caused by syphilis (cases 25 and 26) the polydipsia and polyuria disappeared after satisfactory therapy.

In cases in which specific therapy indicated by the etiologic factor was not tried or was unsuccessful, solution of posterior pituitary gave symptomatic relief. Of 23 cases in which this substance was given hypodermically, a good response was obtained in 21, a moderate response in 1 and a poor response in 1 (table 4). In the case in which the response was poor (case 7), however, the trial was inadequate, as only three injections of solution of posterior pituitary, 1 cc. each, were given before use of the drug was discontinued. In none of these cases was any severe or unfavorable reaction recorded. Of 10 cases in which solution of pitressin was given intranasally, a good response was obtained in 8, a moderate response in 1 and a poor response in 1. In 1 case in which intranasal application of a solution of pitressin produced a good response, this mode of administration had to be discontinued because of severe nasal irritation (case 24). Of 8 cases in which pitressin was given intranasally as a jelly, there were a moderate response in 2 and a poor response in 6. It is apparent that the pitressin was absorbed poorly from the jelly, or not at all. Otherwise there should have been a good therapeutic result. In only 4 cases was pitressin tannate in oil given intramuscularly. Results were fairly good in each case, injections being required once a day in 2 cases, once every other day in 1 case and once every third day in 1 case. Powdered posterior pituitary as a nasal insufflation was tried in only 1 case, and the follow-up observation was inadequate, so that results could not be evaluated. In case 21 the polyuria and polydipsia diminished when the patient was given a low salt diet, although he continued to need posterior pituitary.

In view of reports that the thyroid has an important function in maintaining the diuretic effect of the anterior lobe of the pituitary, it is of interest that in spite of clinical evidence of hypopituitarism and hypothyroidism, with basal metabolic rates of —17 and —30 per cent respectively, in cases 6 and 9, there was definite evidence of diabetes insipidus. Thyroid given in case 6 slightly decreased, rather than increased, the polydipsia and polyuria.

COMMENT

Diabetes insipidus is a symptom complex, produced by damage of the supraopticohypophysial tract, and is not a specific etiologic entity. This fact is too little recognized by the medical profession in general. Any patient with symptoms of diabetes insipidus deserves the most careful study in an attempt to determine the specific pathologic changes responsible for the symptoms. Fink,[37] in collecting 107 postmortem reports of cases of diabetes insipidus in man, found that in 63 per

37. Fink, E. B.: Diabetes Insipidus: A Clinical Review and Analysis of Necropsy Reports, Arch. Path. 6:102 (July) 1928.

cent the disease was due to a tumor at the base of the brain or in the posterior cranial fossa; in 13 per cent, to a syphilitic process, either basal meningitis or a gumma, in or near the hypophysis; in 6 per cent, to a tuberculoma or tuberculous meningitis at the base of the brain; in 8 per cent, to a nonsyphilitic inflammatory process in the same location, and in 10 per cent, to traumatic injuries. The term "idiopathic" diabetes insipidus merely indicates that the pathologic cause was undetermined before death or that the polydipsia and polyuria had a possible psychic origin. The possibility of psychogenic polydipsia and polyuria can be eliminated by a prolonged urine concentration test whenever diabetes insipidus is suspected. As polyuria is primary and polydipsia is secondary in diabetes insipidus, a patient with true diabetes insipidus will continue to have a large volume of urine of low specific gravity, with resultant dehydration and loss of weight during such a test.

Warkany and Mitchell,[38] in listing the causes of diabetes insipidus in children, included idiopathic or hereditary factors, trauma, encephalitis, tuberculosis, syphilis, xanthomatosis, tumors and other rare and unclassified factors. In 1 of the 70 cases studied by Blotner [39] there was a family history of diabetes insipidus. There was no such history in any of the 42 cases included in this group. Baker and Craft [40] reported a case of diabetes insipidus in which postmortem examination showed isolated lesions completely destroying the supraoptic nuclei bilaterally, with resultant destruction of the neurohypophysis. Occasional cases of idiopathic diabetes may be due to such localized atrophy of the supraopticohypophysial tract. Dandy [41] reported a case of permanent diabetes insipidus with onset immediately after the pituitary stalk was cut. In cases of diabetes of traumatic origin laceration of the stalk is the lesion most likely to produce the symptoms. Rand and Patterson [42] reported 6 cases of traumatic origin. Cases of diabetes insipidus of inflammatory origin associated with acute purulent sinusitis and following infection of the middle ear have recently been reported.[43] Biggart [44] described 3 cases of diabetes insipidus with postmortem examinations—the condition being of post-traumatic, metastatic and encephalitic origin respectively. As diabetes insipidus was the first symptom of neoplasm in cases 3 and 4, the case described by Bernstein, Moore and Fishbach [45] is of interest; in this case diabetes insipidus was the first symptom of bronchogenic carcinoma. These authors concluded:

> In the absence of conclusive evidence as to the etiologic factor in a case of diabetes insipidus, it is suggested that a masked malignant process be suspected, that an effort be made to establish the primary source and that, on an empiric basis, irradiation be given to the hypothalamicohypophysial area.

In addition to generalized carcinomatosis, medulloblastoma, Ewing's tumor, round cell sarcoma suggesting unpigmented melanotic sarcoma and carcinoma of the breast, which resulted in diabetes insipidus in cases here reported, metastases from bronchogenic carcinoma, primary carcinoma of the lung, hypernephroma and carcinoma of the stomach have also been reported as etiologic factors.[46] Diabetes insipidus, associated with diabetes mellitus, has been produced by eosinophil tumors of the anterior lobe of the pituitary, with resultant damage of the pars nervosa.[47] Diabetes insipidus has also been associated with pregnancy, but there is no consistency in the relation.[48] Blotner and Kunkel [48c] suggested that in the case of such a complication the diuresis

38. Warkany, J., and Mitchell, A. G.: Diabetes Insipidus in Children, Am. J. Dis. Child. **57**:603 (March) 1939.

39. Blotner, H.: The Inheritance of Diabetes Insipidus, Am. J. M. Sc. **204**:261 (Aug.) 1942.

40. Baker, A. B., and Craft, C. B.: Bilateral Localized Lesions in the Hypothalamus with Complete Destruction of the Neurohypophysis in a Pituitary Dwarf with Severe Permanent Diabetes Insipidus, Endocrinology **26**:801 (May) 1940.

41. Dandy, W. E.: Section of the Human Hypophyseal Stalk: Its Relation to Diabetes Insipidus and Hypophyseal Functions, J. A. M. A. **114**:312 (Jan. 27) 1940.

42. Rand, C. W., and Patterson, G. H.: Traumatic Diabetes Insipidus: Report of Six Cases, Bull. Los Angeles Neurol. Soc. **2**:163 (Dec.) 1937.

43. Weinstein, E. A., and Spingarn, C. L.: A Case of Diabetes Insipidus of Inflammatory Origin, Treated with Roentgen Rays, J. Mt. Sinai Hosp. **7**:90 (July-Aug.) 1940. Yaskin, J. C.; Lewey, F. H., and Schwarz, G.: Diabetes Insipidus and Other Unusual Complications of Acute Purulent Sinusitis: Clinicopathologic Study of a Case, Arch. Neurol. & Psychiat. **48**:119 (July) 1942.

44. Biggart, J. H.: Diabetes Insipidus, Brain **58**:86 (March) 1935.

45. Bernstein, M.; Moore, M. T., and Fishbach, D. B.: Diabetes Insipidus as a Sign of Metastatic Involvement of the Supraopticohypophysial System, Arch. Int. Med. **62**:604 (Oct.) 1938.

46. Futcher, T. B.: Diabetes Insipidus and Lesions of the Mid-Brain: Report of a Case Due to a Metastatic Tumor of the Hypothalamus, Am. J. M. Sc. **178**:837 (Dec.) 1929. Bernstein, Moore and Fishbach.[45] Fink.[37]

47. Greene, J. A., and Gibson, R. B.: Coexistence of Diabetes Mellitus and Diabetes Insipidus, J. Lab. & Clin. Med. **24**:455 (Feb.) 1939. McPherson, E.: Case of Diabetes Mellitus Associated with Lesions of the Pituitary Body, Glasgow M. J. **131**:220 (May) 1939.

48. (*a*) Hart, S. D., and Breitman, H. B.: Diabetes Insipidus Complicating Pregnancy, Am. J. Obst. & Gynec. **41**:527 (March) 1941. (*b*) McLaren, H. C., and McLeod, M.: A Case of Diabetes Insipidus in Pregnancy, J. Obst. & Gynec. Brit. Emp. **49**:51 (Feb.) 1942. (*c*) Blotner, H., and Kunkel, P.: Diabetes Insipidus and Pregnancy: Report of Two Cases, New England J. Med. **227**:287 (Aug. 20) 1942.

most likely has its origin in the anterior lobe or the placenta. Rutledge and Rynearson [49] reported a case in which diabetes insipidus started abruptly after abortion of a 3 month fetus.

Hand-Schüller-Christian disease has been reported to respond well to roentgen irradiation.[50] As has already been recommended, roentgen therapy should also be used in cases of diabetes insipidus in which the existence of malignant growth is proved or suspected.[45] For patients with diabetes insipidus not responding to therapy specifically indicated by the etiologic factor, substitution of the antidiuretic principle in the form of solution of posterior pituitary or pitressin affords notable symptomatic relief. Various methods of administration of preparations of posterior pituitary have been reported to be successful, including nasal insufflations,[51] intranasal application of a solution of posterior pituitary or of posterior pituitary in the form of jelly, hypodermic injection of solution of posterior pituitary or of pitressin, subcutaneous implantation of pellets of posterior pituitary [52] and intramuscular injection of pitressin tannate in oil.[53] Subcutaneous implantation of pellets was reported to give good therapeutic results, but inflammatory reaction at the site of implantation was so severe that the pellets had to be removed before complete absorption had occurred. Intramuscular administration of pitressin tannate in oil has recently been reported to be the most satisfactory form of therapy. The principal advantage is the slower, more prolonged, absorption of the substance and the resultant decreased frequency of injections. Another reported advantage is the avoidance of disagreeable side effects of hypodermic injection of solution of posterior pituitary, including pallor, headache, palpitation, diarrhea and abdominal cramps.

In a number of cases thyroidectomy was reported to have alleviated the symptoms of diabetes insipidus. Blotner and Cutler [54] expressed the belief that the evidence from their studies justified the application of total thyroidectomy in cases of diabetes insipidus associated with postencephalitic paralysis agitans. However, the evidence that thyroidectomy is indicated in such cases is not conclusive. It would seem that thyroidectomy should be done in cases of diabetes insipidus only when there are other associated symptoms indicating the need of such a procedure. According to Findley,[55] although ablation of the thyroid was no more effective in reducing the output of urine than a low salt diet, it increased the patient's reactivity to pitressin and diminished his diuretic response to sodium chloride. After checking the chloride levels of the blood and urine in 22 cases of diabetes insipidus, Blotner concluded that patients with diabetes insipidus maintain a normal chloride balance when they take the ordinary amount of salt in their diet.[56] There is evidence that patients with diabetes insipidus tend to maintain polyuria at a minimum level when they remain on a low salt diet.

SUMMARY AND CONCLUSIONS

On the basis of a report of the important features in 42 cases of diabetes insipidus at the University Hospital, in 34 of which the etiologic factors were clinically or pathologically determined, it is pointed out that diabetes insipidus is a symptom complex produced by injury to the supraopticohypophysial tract, and not a specific etiologic entity. In any case of diabetes insipidus thorough and repeated examinations should be made to determine the etiologic factors. Urine concentration tests indicate that patients with diabetes insipidus receiving a limited intake of fluid continue to secrete urine of low specific gravity, with resultant loss of body weight. In any case in which such a response is obtained the diagnosis of organic damage along the supraopticohypophysial tract should be made.

Ideally, therapy in any case of diabetes insipidus should be directed toward the etiologic factor. Thus, in some cases of neoplasm of the hypothalamus and pituitary and of Hand-Schüller-Christian disease a good response to roentgen irradiation is obtained, and antisyphilitic therapy corrects the diabetes insipidus resulting from

49. Rutledge, D. I., and Rynearson, E. H.: Diabetes Insipidus: Treatment by Insufflations of Powdered Posterior Pituitary Substance, Proc. Staff Meet., Mayo Clin. **14**:441 (July 12) 1939.

50. Sosman, M. C.: Xanthomatosis (Schüller's Disease; Christian's Syndrome): A Report of Three Cases Treated with Roentgen Rays, Am. J. Roentgenol. **23**:581 (June) 1930. Warkany and Mitchell.[38]

51. Smith, F. M.: Treatment by Intranasal Sufflation of Posterior Lobe Powder, J. A. M. A. **102**:660 (March 3) 1934. Rutledge and Rynearson.[49]

52. Greene, J. A., and January, L. E.: Efficacy of Pellets of Posterior Hypophysis and of Pitressin in Oil in Diabetes Insipidus, Proc. Soc. Exper. Biol. & Med. **44**:217 (May) 1940.

53. Greene and January.[52] Thorn and Stein.[31e] Sanders, C. R.: The Treatment of Diabetes Insipidus by Pitressin Tannate in Oil, Lahey Clin. Bull. **2**:244 (April) 1942. Blotner, H.: Pitressin Tannate in Oil in the Treatment of Diabetes Insipidus, J. A. M. A. **119**:995 (July 25) 1942.

54. Blotner, H., and Cutler, E. C.: Total Thyroidectomy in the Treatment of Diabetes Insipidus, J. A. M. A. **116**:2739 (June 21) 1941.

55. Findley, T., Jr.: Thyroid-Pituitary Relationship in Diabetes Insipidus, Ann. Int. Med. **11**:701 (Nov.) 1937.

56. Blotner, H.: Blood and Urine Chlorides in Twenty-Two Cases with Diabetes Insipidus, Am. J. M. Sc. **202**:222 (Aug.) 1941.

syphilis. As diabetes insipidus is not infrequently the first symptom in cases of neoplasm, occurring eight months and six years before other evidence of the malignant growth in 2 of the cases reported here, roentgen irradiation of the hypothalamico-hypophysial region may well be worth while when the cause of the diabetes is undetermined.

Of the various methods of administration of posterior pituitary as replacement therapy in the absence of the antidiuretic principle, intramuscular injection of pitressin tannate in oil seems the most desirable at present. Intranasal application of pitressin in jelly was the least satisfactory of the methods tried. Use of a low salt diet as an adjunct to other therapy may be worth a trial in any case of diabetes insipidus. Thyroidectomy should not be performed for diabetes insipidus unless there are other specific indications for the procedure.

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DISEASE OF THE MITRAL VALVE

ITS EFFECT ON THE PATTERN OF THE ELECTROCARDIOGRAM

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Enlargement of the left auricle of the heart due to rheumatic mitral stenosis is a well recognized occurrence. Numerous reports indicate that extreme dilatation is not uncommon,[1] while lesser degrees of enlargement are regularly observed either roentgenologically [2] or at the autopsy table.[3] Auricular hypertrophy may also be reflected in the electrocardiogram. Einthoven [4] was the first to point out the significance of the auricular complex. Its frequent distortion in mitral stenosis has been noted for a generation.[5] In recent years the work of Master and others [6] has again brought into prominence the possible value of electrocardiographic changes in confirming the clinical diagnosis of disease of the mitral valve. It is the purpose of the present communication to evaluate the electrocardiographic changes commonly recognized in disease of the mitral valve with particular reference to such diagnostic value as they may possess. This study is particularly pertinent inasmuch as universally recognized standards of abnormality of the P wave and deviation of the axis do not exist.

SELECTION OF MATERIAL AND METHOD OF STUDY

During a period of approximately one year a group of subjects was examined at the National Naval Medical Center, Bethesda, Md., with regard to the possibility of their having mitral valve disease. Many of the subjects were candidates for the Navy referred by procurement centers, where the obviously functional murmurs were eliminated. The bulk of the series was, therefore, composed of subjects with systolic murmurs of borderline significance. There were, however, some civilians whose examinations were not conducted for military purposes, among whom definite valvular disease was encountered. The entire group was examined clinically in meticulous detail, and in almost every case studied by means of fluoroscopy or roentgenograms. Examinations were made by two or more physicians, and in a few instances, when opinions differed, a subject was eliminated from the series before the electrocardiographic analysis was commenced.

Before classification as to degree of valvular involvement, carefully standardized electrocardiograms of the entire series were reviewed and a master chart prepared.

The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

1. Nichols, C. F., and Ostrum, H. W.; Unusual Dilatation of the Left Auricle. Am. Heart J. **8**:205-216, 1932. Emanuel, J. G.: Extreme Dilatation of the Left Auricle, Lancet **1**:591-593, 1923. Bach, F. and Keith, T. S.; Enlargement of the Left Auricle of the Heart, ibid. **2**:766-767, 1929. East, C. F. T.: Great Dilatation of the Left Auricle, ibid. **1**:1194-1196, 1926. Shaw, H. B.: Horizontal Dilatation of the Left Auricle, ibid. **2**:493-495, 1924. Holt, E.: Deformity of the Chest Associated with Extreme Dilatation of the Left Auricle: Report of Two Cases, Am. Heart J. **9**:363-369, 1934.

2. Steel, D.: Roentgenological Findings in Mitral Stenosis and Insufficiency, Am. J. Roentgenol. **21**: 220-226, 1929. Cookson, H.: Notes on the X-Ray Diagnosis of Mitral Stenosis, Lancet **1**:1344-1347, 1929. Chamberlain, W. E., and Dock, W.: Motion of the Heart in Disease of the Mitral Valve: Cinematographic Roentgen Ray Studies, Arch. Int. Med. **40**:521-531 (Oct.) 1927. Roesler, H.: Clinical Roentgenology of the Cardiovascular System, Springfield, Ill., Charles C Thomas, Publisher, 1937.

3. MacCallum, W. G.: A Textbook of Pathology, ed. 6, Philadelphia, W. B. Saunders Company, 1937, p. 467. Karsner, H. T.: Human Pathology, ed. 5, Philadelphia, J. B. Lippincott Company, 1938, p. 445. Boyd, W.: The Pathology of Internal Diseases, ed. 3, Philadelphia, Lea & Febiger, 1940, p. 48.

4. Einthoven, W.: Weiteres über das Elektrokardiogram, Arch. f. d. ges. Physiol. **122**:517-584, 1908.

5. (*a*) White, P. D., and Burwell, C. S.: The Effects of Mitral Stenosis, Pulmonic Stenosis, Aortic Regurgitation and Hypertension on the Electrocardiogram, Arch. Int. Med. **34**:529-532 (Oct.) 1924. (*b*) White, P. D., and Bock, A. V.: Electrocardiographic Evidence of Abnormal Ventricular Preponderance and of Auricular Hypertrophy, Am. J. M. Sc. **156**:17-19, 1918. (*c*) Pardee, H. E. B.: Clinical Aspects of the Electrocardiogram, ed. 4, New York, Paul B. Hoeber, Inc., 1941, p. 78. (*d*) White, P. D.: Heart Disease, ed. 2, New York, The Macmillan Company, 1937, p. 123. (*e*) Ashman, R., and Hull, E.: Essentials of Electrocardiography, ibid., 1937. (*f*) Durant, T. M. The Heart in Pulmonary Disease, in Stroud, W. D.: Diagnosis and Treatment of Cardiovascular Disease, Philadelphia, F. A. Davis Company, 1940, p. 229.

6. (*a*) Berliner, K., and Master, A. M.: Mitral Stenosis: A Correlation of Electrocardiographic and Pathologic Observations, Arch. Int. Med. **61**:39-59 (Jan.) 1938. (*b*) Master, A. M.: The Electrocardiogram and X-Ray Configuration of the Heart, ed. 2, Philadelphia, Lea & Febiger, 1942. (*c*) Katz, L. N.; Goldman, A. M.; Langendorf, R.; Kaplan, L. G., and Killian, S. L.: The Diagnostic Value of the Electrocardiogram Based on an Analysis of One Hundred Forty-Nine Autopsy Cases, Am. Heart. J. **24**:627-653, 1942.

On this chart were recorded the names of the subjects without their diagnoses. The following data were then added: the heights of P_1, P_2 and P_3, the width of the widest P wave in any lead, the number of leads in which notching of the P wave was encountered and the number of leads in which deep notching occurred. Deep notching was recorded when the notch returned halfway or more to the base line. The amplitudes of the R and S waves of the standard leads were noted, and from those of leads I and III the angle of the electrical axis was determined by the method of Carter, Richter and Greene.[7] Preliminary study had shown that this method gave results almost identical with those obtained by the original Dieuaide method, based on leads I and III,[8] and entirely comparable to those obtained by the modified Dieuaide method,[5c] which utilized leads I and II.

After the electrocardiographic data were recorded, the subjects were grouped on the basis of physical findings, as follows:

Group I: Patients with functional murmurs. This group included subjects who had short or transient, blowing systolic murmurs, with or without a limited degree of transmission. It also included a few subjects with very short, rough, late systolic murmurs.

Group II: Patients with mitral insufficiency. This group included subjects who had prolonged systolic murmurs which masked the first sound or which persisted throughout the whole of systole, which were unduly harsh or which had a high-pitched "sea gull" overtone. The presence of significant arteriosclerosis was eliminated because of the youth of the subjects. Presumably, therefore, these subjects were suffering from rheumatic valvular disease without sufficient narrowing of the mitral lumen to produce true stenosis.

Group III: Patients with mitral stenosis (inclusive), with or without clinical evidence of involvement of other valves. In this group were included all subjects with unmistakable presystolic murmurs indicative of mitral stenosis.

Group IV: Patients with mitral stenosis (uncomplicated), without clinical evidence of involvement of other valves. This group was separated from group III because of the theoretic possibility that a large left ventricle associated with disease of the aortic valve might affect the size of the mitral valve ring and hence the left auricle, and also because of the effect of a large left ventricle on axis deviation.

TABLE 1.—*Heights of P Waves in Standard Leads**

Group	Age		Number of Cases	Height of P_1		Height of P_2		Height of P_3	
	Range	Mean		Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Control	13-61	26	100	0.68 ± 0.07	0.29 ± 0.02	1.56 ± 0.16	0.47 ± 0.03	0.87 ± 0.09	0.59 ± 0.04
Functional murmurs	9-61	25	97	0.65 ± 0.07	0.27 ± 0.02	1.47 ± 0.15	0.62 ± 0.04	0.88 ± 0.09	0.72 ± 0.05
Functional murmurs	16-32	22	66	0.61 ± 0.06	0.24 ± 0.02	1.46 ± 0.18	0.62 ± 0.05	0.90 ± 0.11	0.79 ± 0.07
Mitral insufficiency	16-52	28	43	0.63 ± 0.10	0.25 ± 0.03	1.48 ± 0.23	0.60 ± 0.06	0.89 ± 0.14	0.74 ± 0.08
Mitral insufficiency	16-35	23	30	0.65 ± 0.12	0.29 ± 0.04	1.40 ± 0.26	0.60 ± 0.08	0.74 ± 0.14	0.79 ± 0.10
Mitral stenosis (inclusive)	18-49	31	22	0.83 ± 0.18	0.35 ± 0.05	1.97 ± 0.42	0.41 ± 0.06	1.20 ± 0.26	1.07 ± 0.16
Mitral stenosis (uncomplicated)	18-49	31	16	0.89 ± 0.22	0.36 ± 0.06	2.28 ± 0.56	1.38 ± 0.24	1.36 ± 0.34	1.08 ± 0.19

* Lead II is the most significant. Lead I shows comparatively little change between the groups, while in lead III the standard deviation is relatively much higher than in lead II. (Variations from the mean and from the standard deviation are expressed in standard error.)

TABLE 2.—*Width of Widest P Wave in Any Standard Lead and Direction of Electrical Axis**

Group	Number	Width of P		Axis Deviation	
		Mean	Standard Deviation	Mean	Standard Deviation
Control	100	0.093 ± 0.009	0.012 ± 0.001	63.9 ± 6.4	21.1 ± 1.5
Functional murmurs	97	0.089 ± 0.009	0.015 ± 0.001	65.0 ± 6.6	27.3 ± 2.0
Functional murmurs (16-32)	66	0.088 ± 0.011	0.015 ± 0.001	67.6 ± 8.3	23.1 ± 2.0
Mitral insufficiency	43	0.097 ± 0.015	0.013 ± 0.001	68.8 ± 10.5	29.0 ± 3.1
Mitral insufficiency (16-35)	30	0.094 ± 0.017	0.014 ± 0.002	71.4 ± 13.1	27.7 ± 3.6
Mitral stenosis (inclusive)	22	0.105 ± 0.022	0.015 ± 0.002	71.2 ± 15.1	28.5 ± 4.3
Mitral stenosis (uncomplicated)	16	0.106 ± 0.026	0.017 ± 0.003	82.1 ± 20.5	20.6 ± 3.6

* P waves are significantly wider in the groups with mitral stenosis than in the control groups. Although the mean angle of the electrical axis is significantly increased in mitral stenosis, the dispersion is sufficiently great to obviate any diagnostic value inherent in this finding. (Variations from the mean and from the standard deviation are expressed as standard error.)

Tricuspid stenosis may have been present in some of the patients with mitral stenosis. It occurs in approximately 9 per cent of rheumatic hearts found at autopsy [9] but can rarely be recognized by clinical means.

A control series of normal electrocardiograms was also studied. These were made from subjects comparable in age to those of the other groups. These persons had been referred to the heart disease station for various routine purposes but in no instance for the evaluation of a murmur. Many of them were studied as a routine precaution before fever therapy for gonorrheal infections.

After measurement of the electrocardiograms and classification of the subjects, data regarding the P

7. Carter, E. P.; Richter, C. P., and Greene, C. H.: A Graphic Application of the Principle of the Equilateral Triangle for Determining the Direction of the Electrical Axis of the Heart in the Human Electrocardiogram, Bull. Johns Hopkins Hosp. **30**:162-167, 1919.

8. Dieuaide, F. R.: The Determination and Significance of the Electrical Axis of the Human Heart, Arch. Int. Med. **27**:558-570 (May) 1921.

9. Smith, J. A., and Levine, S. A.: The Clinical Features of Tricuspid Stenosis, Am. Heart J. **23**:739-760, 1942. Berliner and Master.[6a]

waves and axis deviation of the various clinical groups were tabulated and arranged (tables 1, 2 and 3). Inasmuch as these tables showed age to be unimportant, this factor was not considered in subsequent analyses.

control electrocardiograms and those from the subjects with functional murmurs were combined into one group (figs. 1 and 2) because the tabulation had shown them to be statistically similar. In order to keep subsequent

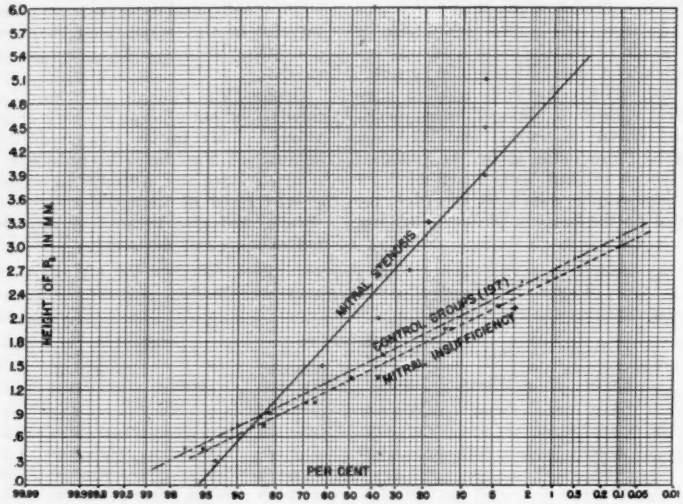

Fig. 1.—Frequency distribution of the height of P_2. Height is recorded along the ordinate and the per cent greater than any indicated height along the abscissa. Note that waves 3 mm. or higher are anticipated from this series for 23 per cent of patients with mitral stenosis, 0.1 per cent of subjects with mitral insufficiency and in 0.2 per cent of controls.

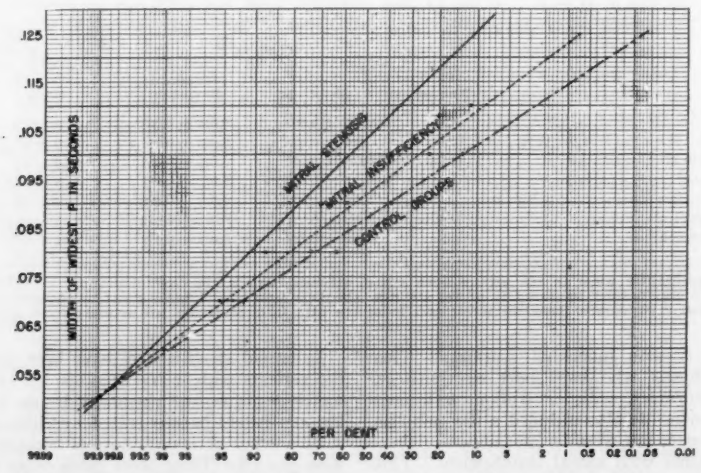

Fig. 2.—Frequency distribution of the width of P waves. Width is recorded along the ordinate and the per cent greater than any indicated width along the abscissa. Note that waves 0.12 second in width or over are anticipated for 18 per cent of patients with mitral stenosis, 2 per cent of patients with mitral insufficiency and 0.3 per cent of controls.

The tabulated data revealed the likelihood that the height of P_2 (table 1) and the width of the widest P wave (table 2) were of some diagnostic importance and this led to the further study of these measurements. The

graphs as simple as possible, only one group of subjects with mitral stenosis (the uncomplicated group) was included. The cumulative percentages of height or width of the P wave were then plotted along the ordinate on

arithmetical probability graph paper (figs. 1 and 2). With this type of graph paper a straight line represents a normal distribution of each sample.[10]

TABLE 3.—*Notching of P Wave**

Group	Number	Notching of P Wave: One Lead or More	Notching of P Wave: More Than One Lead	Deep Notching of P Wave: One Lead or More	Deep Notching of P Wave: More Than One Lead
Control	100	50.0%	35.0%	6.0%	2.0%
Functional murmurs	100	47.0%	30.0%	8.0%	4.0%
Mitral insufficiency	43	70.0%	44.1%	16.3%	7.0%
Mitral stenosis (inclusive)	22	50.0%	31.8%	18.2%	9.1%
Mitral stenosis (uncomplicated)	16	56.1%	43.8%	25 %	12.5%

* Deep notching was considered to be present when the apex of the notch returned half way to the base line. Although there is a trend toward more frequent notching in the abnormal than in the control groups, this trend is of limited diagnostic value.

The arithmetical probability of waves exceeding any given height (fig. 1) or width (fig. 2) could therefore be read directly from the abscissa.

A composite graph (fig. 3) was also prepared. On this were recorded: (*a*) the percentage of subjects in each clinical group whose only abnormality was a P_2 3 mm. or more in height; (*b*) the percentage whose only abnormality was a P wave 0.12 second or more in duration; (*c*) the percentage whose only abnormality was deep notching of the P wave in two leads or more and (*d*) the percentage with any two or more of these characteristics. The reasons for choosing these particular values are discussed below.

ANALYSIS OF DATA

The heights of the P waves were studied after reference to table 1. It was concluded that the increased height of P_2 in mitral stenosis is of definite statistical significance. The increase in

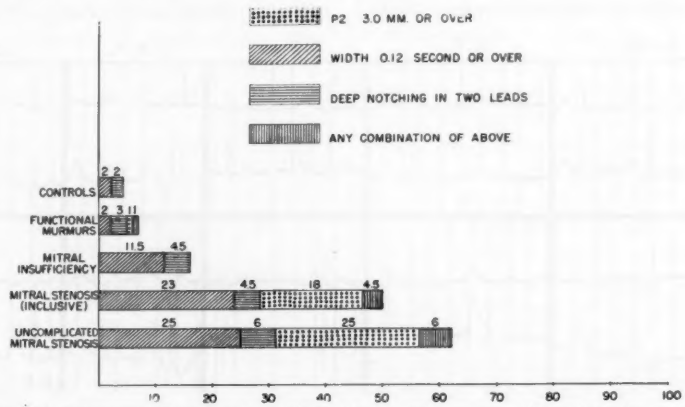

Fig. 3.—Percentage of abnormal P waves in each of the several groups. Note that the percentage of P waves 3 mm. or more in height and 0.12 second or more in width is definitely increased in mitral stenosis.

lead I was too small to be of importance, while in lead III the dispersion was too great. In all cases studied, whatever the type of lesion present, there was only 1 instance in which the height of P_3 exceeded that of P_2. From the figures plotted on arithmetical probability graph paper it was possible to make a direct comparison between the heights of P_2 in this study and the criteria of abnormality advocated by several authors.

Pardee [5e] found a P wave 2 mm. or more in height in the electrocardiograms of 75 per cent of patients with mitral stenosis, an observation which corresponds with an arithmetical probability of 53 per cent for such patients on the basis of the present study (fig. 1). Ashman and Hull [5e] found that 2 per cent of their control group had P waves 2.5 mm. or more in height, an incidence which corresponds with an arithmetical probability of 2.5 per cent (fig. 1). White [11] found that P waves 3 mm. or more in height were almost invariably associated with heart disease, in most instances mitral stenosis.

10. A representative series from a normally distributed group is said to follow a normal frequency distribution (bell-shaped curve). Plotted on ordinary graph paper, with size along the abscissa and the number of items of each size along the ordinate, such a normal frequency distribution produces a curve of the characteristic bell shape. If the same distribution is plotted on ordinary graph paper with size again along the abscissa but with the number exceeding any given size along the ordinate, the result is an S-shaped curve (ogive) which is steep near the median. On arithmetical probability graph paper, however, the figures along the ordinate are separated more widely at the two ends of the scale than in the middle, in such a way that the S-shaped curve of a normal frequency distribution appears as a straight line. This type of paper has several advantages over ordinary graph paper: 1. It affords a simple means of determining whether items of varying sizes follow a normal frequency distribution. 2. It affords a simple means of determining the median value, the standard deviation and the percentage expected to fall within any given range. 3. It is readily adaptable to the charting of several distribution curves on one piece of paper. The use of arithmetical probability paper has been discussed by G. C. Whipple (in Vital Statistics, ed. 2, New York, John Wiley & Sons, Inc., 1923, chap. 13). (In figures 1 and 2 the abscissa and the ordinate are reversed for editorial reasons.)

11. White and Bock,[5b] White.[5d]

It is anticipated on the basis of figure 1 that such waves occur in the tracings of only 0.2 per cent of control subjects. White's figure was therefore chosen for the construction of figure 3.

The mean figures for the heights of P_1, P_2 and P_3 in the electrocardiograms of the control group and of the group with mitral stenosis were in close agreement with those of Ashman and Hull. Those of the control group corresponded with a similar group reported by Wilson.[12]

Reference to table 2 indicated that the width of the widest P wave in any standard lead was significantly greater in mitral stenosis than in the control groups. From figure 2 it was found that P waves 0.12 second or more in duration were anticipated for 18 per cent of patients with mitral stenosis, 2 per cent of patients with mitral insufficiency and 0.3 per cent of controls. Waves of this width were therefore considered abnormal in the preparation of figure 3.

Superficial notching of the P wave occurred so frequently as to be of no importance. Deep notching in one lead or more occurred in 6 per cent of the control group and in 8 per cent of the group with functional murmurs. Deep notching in two leads or more appeared in 2 per cent of the control group and in 12.5 per cent of the group with mitral stenosis. It was therefore felt that even deep notching in two leads was a doubtful criterion of abnormality. For purposes of illustration, however, it was employed in the preparation of figure 3.

A review of the data regarding the direction of the electrical axis indicated that there was no significant difference between the control group, the group with functional murmurs and the group with mitral insufficiency. The mean angle for these groups was 65 degrees. Patients with mitral stenosis showed a statistically significant increase toward the right, the mean being 82 degrees, but the variability was so great as to nullify any diagnostic importance which this finding might imply. The average angle in the larger (inclusive) group with mitral stenosis was 71 degrees, somewhat less than in uncomplicated mitral stenosis. This finding is explained by an admixture of large left ventricles secondary to disease of the aortic valve.

COMMENT

Tall P waves in mitral stenosis occur with significant frequency, but they do not occur as often as one would expect if left auricular hypertrophy alone invariably produced such changes.[3] An electrocardiographic review by Berliner and Master [6a] of cases in which autopsies were performed illuminates this problem. These workers found that in uncomplicated mitral stenosis the height of the P waves was not materially increased. The average height was 1.63 mm. In the case of hearts which showed both mitral stenosis and tricuspid stenosis, however, the average height of the P waves was 2.62 mm. In such instances both auricles were hypertrophied. In the groups of persons with mitral stenosis in the present study the possibility exists that a few subjects with tricuspid stenosis may have been included. Smith and Levine [9] found that 9.4 per cent of autopsied hearts with rheumatic valvular disease showed tricuspid stenosis, and they found a similar change in 14 per cent of hearts with mitral stenosis in which the aortic valve was not involved. This incidence of tricuspid stenosis is comparable to that derived

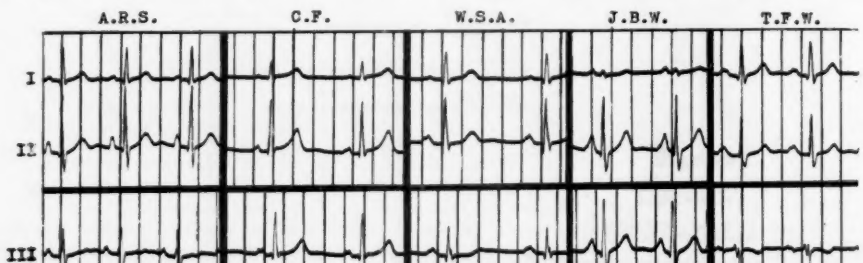

Fig. 4.—Characteristic P waves. A. R. S.: The P wave in lead II is over 2.5 mm. tall and those in leads III and IV are slightly notched. C. F.: The P wave in lead II is slightly notched and that in lead III deeply notched. W. S. A.: The P waves in leads II and III are 0.12 second wide; their rounded shape encompasses a large area. J. B. W.: The P wave in lead II is 4 mm. high, and that in lead III is 0.12 second wide. T. F. W.: The P wave in lead II is 0.12 second wide, and those in all leads are notched.

12. Wilson, F. N.: Recent Progress in Electrocardiography and the Interpretation of Borderline Electrocardiograms, Proc. Life Insur. M. Dir. America. **24**: 96-156, 1938.

from Berliner and Master's [6n] series and also to that reported by Osler and Gibson.[13]

It has commonly been thought and recently emphasized by Ashman and Hull [5e] and by Durant [5f] that in mitral stenosis the amplitude of the P waves is increased in leads I and II, while in auricular hypertrophy secondary to pulmonary disease or congenital pulmonic stenosis the increase in amplitude appears in leads II and III. Reference to table 1 illustrates that in this study, contrary to the customary teaching, the significant increase in the amplitude of the P waves in mitral stenosis occurred in leads II and III, rather than in leads I and II.

The increase in the width of the P wave is a relatively common electrocardiographic change in mitral valve disease. Few wide P waves occur in the electrocardiograms of normal persons, while waves 0.12 second in width occur frequently in the tracings of persons with mitral stenosis. The fact that the absolute widths of the P wave measurements in this study exceed the values reported elsewhere is due to the fact that in this series the widest wave in any lead was measured. There is an appreciable variation in the widths of the P waves in any one lead.

Notching of the P waves occurred in this study with greater frequency than is generally reported. This observation is considered to be due to the use for many of the tracings of a vacuum tube amplifier type of electrocardiograph especially designed to cast a thin string shadow.

The lack of value of axis deviation in the diagnosis of disease of the mitral valve probably is explained by three factors: First, in most cases mitral stenosis is accompanied by some degree of insufficiency, with left ventricular as well as left auricular enlargement. Cases of so-called "pure" mitral stenosis, with an atrophic left ventricle, occur uncommonly. Second, the persons with functional murmurs and the control group were largely recruited from young persons, who have a normal tendency to deviation of the axis to the right. Third, there is a wide variation of the electrical axis both in controls and in persons with mitral stenosis.

The significance of electrocardiographic evidence cannot be entirely reduced to measurements and percentages. The shape of the P wave in itself is probably important as representing area. Large irregular or rounded waves are probably more significant of abnormality than tent-shaped waves of similar height or width. Unfortunately, the area encompassed by P waves does not lend itself readily to planimetric estimation. Examples of variations in the contour of P waves are illustrated in figure 4.

The effect of mitral stenosis on the electrocardiogram is frequently reflected by increased height or width or by deep notching of the P wave. The trends toward these changes are statistically significant, and if sufficiently conservative values are established as criteria of abnormality the changes may be accepted as of corroborative help in diagnosis. It is suggested that P waves 3 mm. or more in height in lead II, 0.12 second or more in width in any lead or deeply notched in two or more leads be considered as abnormal.

13. Osler, W., and Gibson, A. G.: Valvular Diseases of the Heart, in Osler, W.: Modern Medicine, Philadelphia, Lea & Febiger, 1927, vol. 4, chap. 19, pp. 529-558.

SUMMARY

Standardized electrocardiograms from a group of 100 controls, a group of 100 subjects with functional systolic murmurs, a group of 43 subjects with mitral insufficiency and a group of 22 patients with mitral stenosis were analyzed. The criteria considered were the heights of the P waves in the standard leads, the width of the widest P wave in any lead, the degree of notching of the P waves and the leads in which it occurred, and the determination of the direction of the electrical axis. Certain variations in the P waves were found to be of statistical significance, and tentative criteria of abnormality were established. A study of these criteria showed them to be of corroborative but not of specific diagnostic value.

CONCLUSIONS

A group of subjects with functional systolic murmurs showed no difference in their electrocardiographic patterns from a control group of similar age.

Changes occurred in the P waves in some subjects with mitral insufficiency, but these were not sufficiently frequent to be of diagnostic importance.

Patients with mitral stenosis showed a significant percentage of tall P waves (3.0 mm. or more), broad P waves (0.12 second) and P waves which were deeply notched in two or more leads. One or more of these changes occurred in 62 per cent of such patients, as compared with 4 per cent of controls.

The tall P waves in mitral stenosis appeared as a rule in leads II and III, rather than, as is commonly taught, in leads I and II.

The angle of the electrical axis was found to be of no diagnostic value.

Lieutenant (jg) C. E. Curtis (HC), U.S.N., assisted in preparing the statistical material.

VASODEPRESSOR AND CAROTID SINUS SYNCOPE

CLINICAL, ELECTROENCEPHALOGRAPHIC AND ELECTROCARDIOGRAPHIC OBSERVATIONS

GEORGE L. ENGEL, M.D.*; JOHN ROMANO, M.D., AND T. R. McLIN, M.D.‡

CINCINNATI

Syncope, or fainting, is by definition a transient reaction, and only rarely does the physician have an opportunity to make careful observations during a spontaneous episode. Certain types of syncope which may be provoked at will, notably carotid sinus syncope,[1] spontaneous and induced orthostatic hypotension [2] and some rare examples of vagovagal syncope,[3] have been studied extensively. The introduction of the ink-writing electroencephalograph (Grass) offers a method of obtaining continuous simultaneous records of the electrical activity of the brain (electroencephalogram) and of the heart (electrocardiogram) during the syncopal experience and of correlating these with other clinical and physiologic data. In this paper we are reporting on the clinical, electroencephalographic, electrocardiographic and circulatory responses observed during a variety of syncopal reactions, including syncope provoked by venipuncture, by distention of the duodenum, colon, rectum or vagina, by hyperventilation and by carotid sinus reflex. The mechanisms of these various types of syncope will be discussed.

There have been several earlier reports on the electroencephalogram during carotid sinus syncope,[4] and during orthostatic syncope.[4e] The effects of other types of syncope on the electroencephalogram have not yet been studied. Forster, Roseman and Gibbs have reported that slow waves appear during orthostatic syncope but that they are rare in carotid sinus syncope of the circulatory type and do not occur in carotid sinus syncope of the cerebral type. Engel and Margolin,[4b, c] on the other hand, have reported slow waves to be a consistent feature of carotid sinus reflex syncope of both types. An attempt will be made to reconcile these differences.

MATERIAL AND METHODS

Eighteen patients and volunteer subjects were studied. Pertinent clinical data will be presented with each report. In some instances syncope was a chance occurrence in the course of an unrelated experiment. In other instances the clinical history suggested that a certain procedure (for example, distention of viscera or massage of the carotid sinus) would provoke syncope.

A three channel ink-writing electroencephalograph, constructed by Mr. Albert Grass, was used in the studies. One channel was used to record the electrocardiogram. Electrodes were placed on both shoulders, which gives a modified first lead. The electrical activity of the brain was recorded by bipolar tracings from left and right fronto-occipital leads. In these studies no attempts at localization were made other than to compare the two hemispheres. Bipolar leads were used because we have found that with this method artefacts due to movements of the subject and of the examiner are rare, while they are common when monopolar leads are used. Most of the subjects were examined on the tilt table. Before any special syncope-provoking procedure was attempted, the reaction to motionless stand-

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Most of the investigation was carried out in the Medical Clinic of the Peter Bent Brigham Hospital, Boston, and in the Department of Medicine, Harvard Medical School.

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ing for at least ten minutes was tested. The special procedures were initiated when it was clear that the postural response was normal. During the reactions blood pressure was recorded as frequently as was practical, and continuous observations on the color of the skin, sweating, subjective responses and other changes were noted.

RESULTS

VASODEPRESSOR SYNCOPE PROVOKED BY VENIPUNCTURE

This is a common reaction in the experience of all physicians. The clinical picture of progressive pallor, sweating, weakness, faintness, feeble pulse and finally unconsciousness if the subject has not already lowered the head is familiar to all.

CASE 1.—*Clinical Data.*—J. M. was an 18 year old youth who had been discharged from the Marine Corps because of several episodes of syncope. He came to the outpatient department of the Peter Bent Brigham Hospital for reassurance that he did not have epilepsy. He related that he had on six occasions lost consciousness while drilling in the hot weather. All the attacks had occurred while the patient was standing or walking and had been characterized by progressive weakness, faintness, nausea and sweating, followed in a few minutes by buckling of the legs and loss of consciousness. Consciousness returned in a few seconds, and in a few minutes he felt entirely well again.

There was no family history of fits or faints.

The patient was a tall (6 feet, 2 inches [188 cm.]), thin (141 pounds [64 Kg.]) youth who was ill at ease. His physical condition was normal in all other respects.

Experiment.—The patient was studied on the tilt table. When he was recumbent, his pulse rate was 54 and there was rather pronounced sinus arrhythmia. His blood pressure ranged between 102 and 110 mm. during systole, with 70 mm. during diastole. The electroencephalogram was normal.

The patient was then tilted to 70 degrees, and after he had stood motionless for thirteen minutes his pulse rate was 96 and his blood pressure 110 mm. systolic and 72 mm. diastolic. The electroencephalogram was unchanged, and there were no symptoms.

Hyperventilation for three minutes in the erect position resulted in a rather sharp decrease in the frequency of the electroencephalographic waves, an acceleration of the pulse rate to 120 and a fall in blood pressure to 104 mm. systolic and 60 mm. diastolic. The electroencephalogram returned to normal in thirty seconds, and at the end of one minute the blood pressure was 106 mm. systolic and 78 mm. diastolic and the pulse rate was 90. Massage of the right carotid sinus caused the blood pressure to fall to 90 mm. systolic and 78 mm. diastolic and reduced the pulse rate to 60, but there were no symptoms. One minute later the pulse rate was 78 and the blood pressure was 100 mm. systolic and 76 mm. diastolic. The electroencephalogram was still normal, and the patient had no symptoms.

Two minutes later 12 cc. of a 50 per cent solution of dextrose was injected intravenously. About ten seconds after the injection the patient complained of a sense of warmth, which was followed rapidly by weakness, pallor, sweating, faintness and then loss of consciousness. In twenty seconds he flushed and recovered consciousness while still in the erect position. He was immediately returned to the recumbent position. An electroencephalogram and an electrocardiogram were not obtained during this phase of the reaction.

After the patient had been recumbent for two minutes his blood pressure was 110 mm. systolic and 50 mm. diastolic and his pulse rate was 42. One minute later the patient was again tilted to 70 degrees. Pallor quickly appeared, and after three minutes he again complained of weakness and faintness and lost consciousness. Simultaneously the electroencephalogram showed large, high voltage, 2 to 3 per second waves, while the electrocardiogram showed a sinus pause of four seconds followed by ventricular escape. The patient was quickly tilted back, which induced return of consciousness and reappearance of sinus rhythm (cardiac rate 42). The blood pressure was 88 mm. systolic and 48 mm. diastolic. The electroencephalogram rather promptly returned to the presyncope status. The successive changes in the electroencephalogram and electrocardiogram are shown in figure 1.

Comment.—This case illustrates vasodepressor reaction provoked by the simple stimulus of venipuncture. The clinical picture suggested that the primary reaction was a fall in blood pressure which was greatly accentuated by the effects of gravity when the patient was in the erect position. That the disturbance in the circulatory mechanism was not corrected but only ameliorated by the resumption of the recumbent position is shown by the prompt recurrence of the syncopal reaction when the patient was again tilted erect. This delay in recovery is illustrated even more dramatically in the next case. Sinus arrest followed by idioventricular rhythm is not a necessary component of this type of syncope, as will be shown in other examples. The maximum change in the electroencephalogram occurred simultaneously with the loss of consciousness, and the electroencephalogram returned promptly to normal when consciousness was restored.

CASE 2.—*Clinical Data.*—F. B., a 35 year old physician, had a history of frequent syncopal reactions in the past, usually occurring during his first observation of procedures such as venipunctures, minor operations and autopsies.

Experiment.—The postural reactions of the patient were normal. During a venipuncture the subject began to complain of weakness, faintness and sweating and became pale. His blood pressure fell from 125 mm. systolic and 75 mm. diastolic to 60 systolic and 40 diastolic. He was restored to the recumbent position, and in seven minutes the blood pressure returned to 112 mm. systolic and 75 diastolic. He was then tilted to 70 degrees, and in one minute the blood pressure fell to 95 mm. systolic and 60 diastolic and the previous syncopal symptoms recurred. The symptoms promptly disappeared when the patient was recumbent, and the blood pressure returned to 118 mm. systolic and 80 mm. diastolic. After the patient had lain motionless for forty minutes he was again tilted to the erect position. In four minutes the blood pressure was 75 mm. systolic and 25 diastolic and unconsciousness appeared imminent. Recovery was prompt when he was returned to the recumbent position, but after thirty-seven minutes' rest tilting again provoked syncopal symptoms in three and one-half minutes, with a fall in blood pressure to 75 mm. systolic and 45 diastolic. This occurred two hours and ten minutes after the initial syncopal episode. After another period of recumbency, of eleven minutes, the

subject was tilted to the erect position, but on this occasion he was instructed to exercise by jogging in place. After four minutes the blood pressure had fallen slightly (from 125 mm. systolic and 72 diastolic to 118 systolic and 80 diastolic), and there were no symptoms. The patient then sat with his legs dependent, and after five minutes the blood pressure had fallen to 95 mm. systolic and 75 diastolic and mild symptoms had recurred. When the patient resumed exercise, his blood pressure returned to 125 mm. systolic and 75 diastolic and the symptoms subsided. After he had stood fifteen minutes, the blood pressure was still normal. The successive changes in the electrocardiogram and the electroencephalogram are shown in figure 2.

The subject returned to his duties, which involved walking, standing and sitting, and had no untoward symptoms during the subsequent four hours. At the end of that time he was again tilted and was able to stand motionless for eleven minutes without fall in blood pressure and without symptoms.

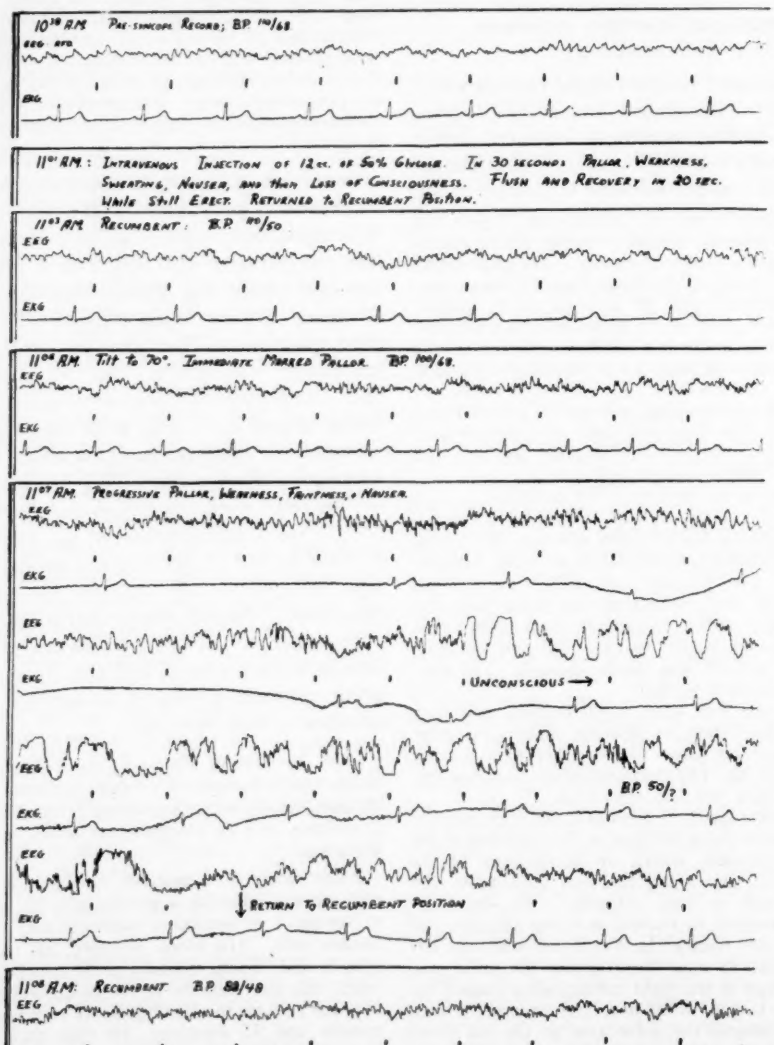
10³⁰ A.M. Pre-syncopal Record; B.P. 120/68
EEG
EKG
11° A.M.: Intravenous Injection of 12 cc. of 50% Glucose. In 30 seconds Pallor, Weakness, Sweating, Nausea, and then Loss of Consciousness. Flush and Recovery in 20 sec. While Still Erect. Returned to Recumbent Position.
11⁰³ A.M. Recumbent: B.P. 110/50
11⁰⁶ A.M. Tilt to 70°. Immediate Marked Pallor. B.P. 100/68.
11⁰⁷ A.M. Progressive Pallor, Weakness, Faintness, & Nausea.
Unconscious
B.P. 50/?
Return to Recumbent Position
11⁰⁸ A.M. Recumbent B.P. 88/48

Fig. 1 (case 1).—Vasodepressor syncope following venipuncture. The first strip shows the normal record before syncope. Syncope developed thirty seconds after a venipuncture. The patient was restored to the recumbent position for three minutes and then tilted to 70 degrees. The fall in blood pressure, the sinus pause followed by ventricular escape and the high voltage slow waves in the electroencephalogram accompanying the syncopal reaction are illustrated. Normal sinus rhythm returned immediately on the patient's resumption of the recumbent position. (The intervals in all records represent one second.)

Comment.—This case demonstrates a number of important points concerning simple vasodepressor syncope: 1. The syncopal symptoms (weakness, faintness, sweating, pallor and nausea) occur during the phase of falling arterial blood pressure. 2. Unconsciousness does not occur unless the blood pressure reaches a critically low point. 3. The circulatory defect that leads to the fall in blood pressure is present regardless of posture, but standing magnifies the depressor phase, presumably through the pooling effect of gravity. 4. The provoking stimulus, in this case venipuncture, initiates a reaction which may continue long after the stimulus has been removed. In this case the reaction could still be demonstrated after two and a half hours. 5. The reaction may be prolonged by allowing the subject to remain motionless, but muscular exercise, on the other hand, seems to counteract it. In this subject even a phase of falling blood pressure could be reversed by jogging in place. The effect of mild exercise in restoring blood pressure may be mechanical (increased muscle tonus) or reflex. The degree to which muscle tonus alone is involved in venous return has not yet been subject to quantitative study. However, since exercise seemed permanently to overcome the reaction, it is tentatively suggested that one effect of exercise is to increase the intensity of certain normal postural circulatory reflexes to a sufficient extent to overcome the circulatory disturbance caused by the original stimulus.

Since this patient was observed, we have seen 2 more examples of vasodepressor syncope prolonged by motionless lying for one to two hours after the initial stimulus and finally overcome by exercise.

These observations suggest that in simple vasodepressor syncope the patient should be encouraged to move about as soon as he has recovered from the initial phase of the reaction.

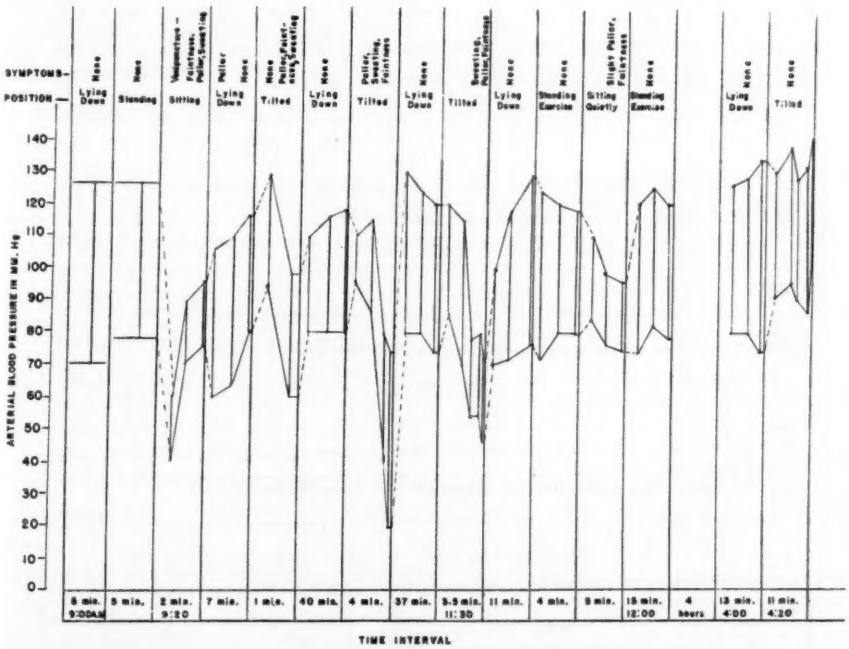

Fig. 2 (case 2).—Prolonged postural maladaptation following simple vasodepressor syncope provoked by venipuncture. During two hours and ten minutes after vasodepressor syncope the subject experienced fall in blood pressure and syncopal symptoms whenever he was tilted to the erect position. Recovery occurred only after exercise. The blood pressure responses are illustrated.

VASODEPRESSOR SYNCOPE PROVOKED BY VISCERAL DISTENTION

Syncope occurring during distention or spasm of hollow viscera is well known to most physicians. Four patients were studied who had in the past experienced syncopal symptoms under such circumstances.

CASE 3.—*Syncope Provoked by Colonic Distention.*

Clinical Data.—J. R., a 34 year old physician in good health, had experienced syncopal symptoms after the insertion of a rectal suppository and twice during severe abdominal distention provoked by decrease in atmospheric pressure in a decompression chamber.

Experiment (fig. 3).—The subject had been studied several times previously on the tilt table and had always

shown normal postural adaptation. In the recumbent position his blood pressure was 112 mm. systolic and 66 diastolic and his pulse rate 66. After he had stood motionless for five minutes, the blood pressure was 116 mm. systolic and 84 diastolic and his pulse rate was 84. A rectal tube was then inserted, and air was introduced under slight pressure (20 to 40 cm. of water by displacement from two bottles) at the rate of 1 liter in five to seven minutes. After 1 liter had been introduced, the pulse rate, blood pressure, electrocardiogram and electroencephalogram were unchanged and the subject was aware only of a sense of slight distention. After 2 liters had been introduced, the blood pressure was 108 mm. systolic and 78 diastolic, the pulse rate was 78, the electrocardiogram and electroencephalogram were unchanged and the subject was experiencing mild to moderate cramps and distention in the lower part of the abdomen. After 3 liters had been introduced, there was no further change but cramps were somewhat more severe. The tube was then clamped off. The subsequent

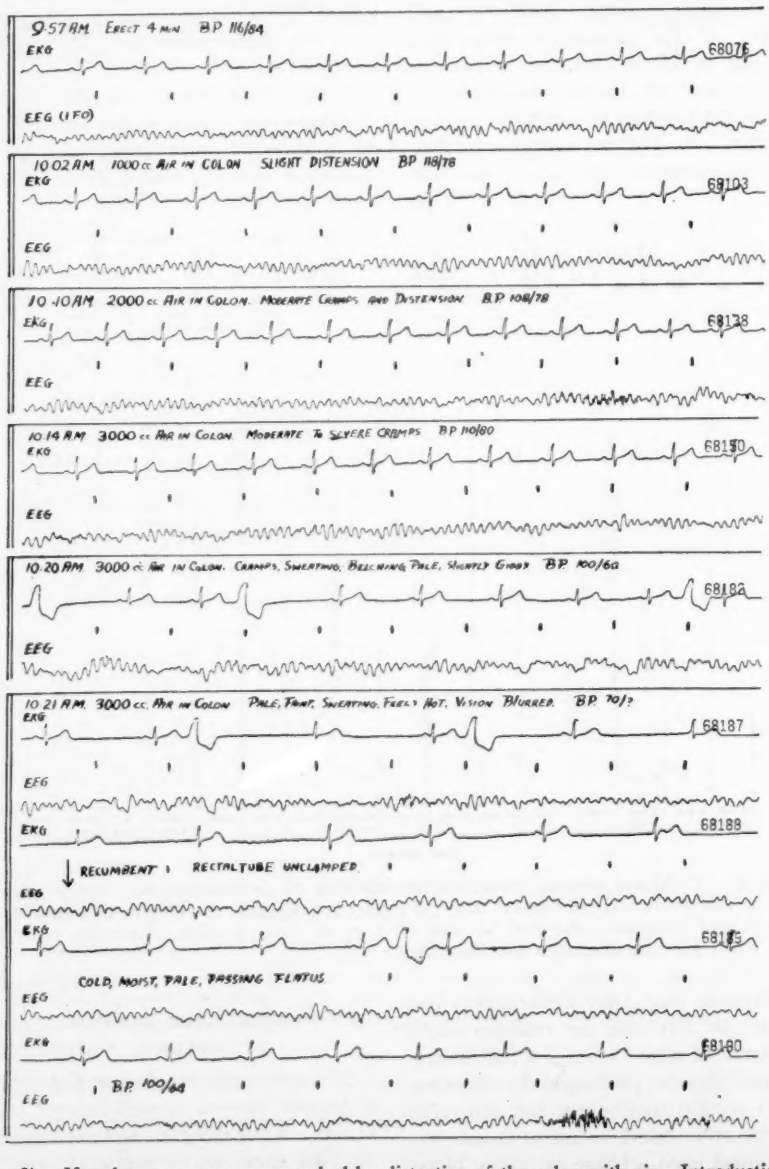

Fig. 3 (case 3).—Vasodepressor syncope provoked by distention of the colon with air. Introduction of 3,000 cc. of air into the large bowel produced cramps, then sweating, pallor, belching, weakness, faintness, fall in blood pressure and ventricular extrasystoles and finally bradycardia (heart rate 36) with mixed sinus arrest, ventricular extrasystoles and ventricular escape. The subject did not lose consciousness, and the electroencephalogram showed no high voltage slow waves.

course is illustrated in figure 3. The subject experienced severe cramps and frequent ventricular extrasystoles. The blood pressure began to fall; the cardiac rate slowed, and there were progressive sweating, pallor, belching, lightheadedness and faintness. When the systolic blood pressure reached 70 mm. (diastolic could not be recorded), the pulse rate was 42 to 68 and the subject was on the verge of loss of consciousness and had blurring of vision. There was sudden bradycardia (pulse rate 36), with a mixture of incomplete sinus arrest, ventricular extrasystoles and idioventricular rhythm. The P wave (auricular beat) sometimes failed to appear; when it did, it bore no relationship to the ventricular complex. The electroencephalogram showed decreased alpha activity and some slowing, to the range of 7 cycles per second. At this point the subject asked to be lowered. With the return to the recumbent position there was prompt rise in the blood pressure, to 100 mm. systolic and 64 diastolic, and restoration of sinus rhythm. The subject was cold, pale and moist, but he improved rapidly as flatus was expelled.

Comment.—This experiment illustrates typical vasodepressor syncope provoked by distention of the colon. The subject did not lose consciousness, and there were no notable changes in the electroencephalogram. In our experience high voltage slow waves do not occur in the absence of distinct changes in consciousness. The other prominent manifestations of vasodepressor syncope, such as sweating, pallor, weakness, nausea, bradycardia and disturbances in rhythm, are reactions occurring during the phase of falling arterial blood pressure and precede the development of unconsciousness, with its associated electroencephalographic changes, by a variable interval. They persist when the subject is recumbent only if the blood pressure remains low.

CASE 4.—*Syncopal Reaction Provoked by Distention of the Rectum.*

Clinical Data.—H. Z., a 28 year old soldier, was referred to us for study of fainting.[5] The patient had always enjoyed good health. He had fainted three times in the past. Eight years earlier, upset over a death in the family, he had fainted while his blood pressure was being taken. One and a half years earlier, while suffering from a local infection, he had fainted. Two weeks earlier he had fainted while retaining an enema. He was seated on the toilet when he began to feel weak, hot, giddy and nauseated. He fell over, striking his head on the floor. He was found unconscious. Examination by Major Roy Swank revealed that the pupils were in the normal position and reacted to light, the eyes moved slowly in the horizontal plane, there was no resistance to movement of the lids and the arms and legs were limp. Deep reflexes were present but diminished, and there were no pathologic reflexes. No convulsive movements were observed, and incontinence had not occurred. The blood pressure was 120 mm. systolic and 80 diastolic, and the pulse rate was 120. The color of the skin was normal. Respiration was somewhat noisy, with short periods of hiccups. After about one hour the patient began to move his extremities slowly, and during the next two hours his level of awareness gradually returned to normal.

Lumbar puncture revealed clear spinal fluid without cells and with normal dynamics (pressure 135 mm. of water). The blood contained 100 mg. of sugar and 38 mg. of urea per hundred cubic centimeters. The urine was normal.

From these observations it was not certain whether the patient had experienced syncope complicated by injury to the head or had had an epileptic seizure. He was not observed during the attack, and there was no family history of epileptic seizures.

Neurologic examination at the time of the study revealed no abnormal conditions. The electroencephalogram was normal.

Experiment.—Postural adaptation was normal. The following experiment was carried out. A balloon made of a rubber condom fastened to a rectal tube was inserted into the rectum. Pressure in the balloon was measured with a water manometer. Air was introduced with a 50 cc. syringe, while the patient was seated in bed. The results of this study are summarized in figure 4.

There was no significant change until 400 cc. of air had been introduced and the pressure in the rectal balloon was 80 cm. of water. At this point the blood pressure and pulse rate began to fall, reaching lows of 70 mm. systolic and 50 mm. diastolic pressure and 54 pulsations respectively. The patient became restless and pale; he sweated and felt somewhat lightheaded. However, the pressure in the balloon slowly fell to 56 cm. of water in the next three minutes, and during this period the blood pressure began to rise somewhat (to 84 mm. systolic and 60 diastolic), although symptoms persisted. An additional 200 cc. of air was introduced, raising the pressure in the balloon to 100 cm. of water. This produced considerable pain, which was followed by a rapid rise in the blood pressure, acceleration of the pulse rate and disappearance of the syncopal symptoms. Release of air from the balloon produced no further change.

The electroencephalogram showed no change during the period of falling blood pressure, and the patient did not lose consciousness.

Comment.—More severe syncopal symptoms undoubtedly would have occurred during this experiment had the subject been standing. The effect of pain was striking. When increased rectal distention produced severe pain, there were a rapid rise in the blood pressure and acceleration of the pulse rate, with prompt amelioration of the symptoms. This reaction suggests that the usual sympathetic response to pain (that is, tachycardia and rise in blood pressure) may counteract vasodepressor syncope. Apparently pain, in the sense of a simple afferent nervous impulse, is not the stimulus for vasodepressor syncope. Of more importance is the psychologic meaning of the painful experience. In this respect the psychologic effects of trauma and mutilation must be appreciated; some persons faint readily on witnessing injury or mutilation without having experienced any pain.

5. This patient was referred to us by Major Roy Swank, Medical Corps, Army of the United States.

CASE 5.—*Syncope Provoked by Distention of the Duodenum.*

Clinical Data.—J. T., a 40 year old egg merchant, had been in good health until two months before he was admitted to the hospital, at which time he began to have attacks of fulness and bloating beneath the left breast, associated with much belching. The first of these attacks was associated with giddiness, unsteadiness, weakness and sweating; the patient was forced to lie down, but he did not lose consciousness. Five weeks later he had a similar episode in which he lost consciousness and fell, striking his head against an automobile bumper. He was unconscious an unknown period and on recovering consciousness had some disturbance in awareness. During the subsequent two weeks he had frequent episodes of pressure and discomfort in the left upper quadrant relieved by belching and sometimes associated with weakness and faintness.

The control electroencephalogram and electrocardiogram were normal. The pulse rate was 78. After the empty balloon had been in place for four and a half minutes without any effect, 60 cc. of air was introduced. This resulted in epigastric distress, belching and cardiac slowing due to sinus pauses. After one minute the balloon was emptied but left in place. In two minutes the patient began to feel vaguely ill, weak and nauseated and showed pallor and sweating. The symptoms progressed rapidly, with ashen pallor, groaning, restlessness, sweating and then unconsciousness, followed by generalized clonic twitching. The electroencephalogram made at this time showed high voltage slow (2 to 4 per second) waves, while the electrocardiogram showed lengthening sinus pauses which finally reached five seconds, followed by ventricular escape. The patient recovered consciousness in the recumbent position but remained in a state of

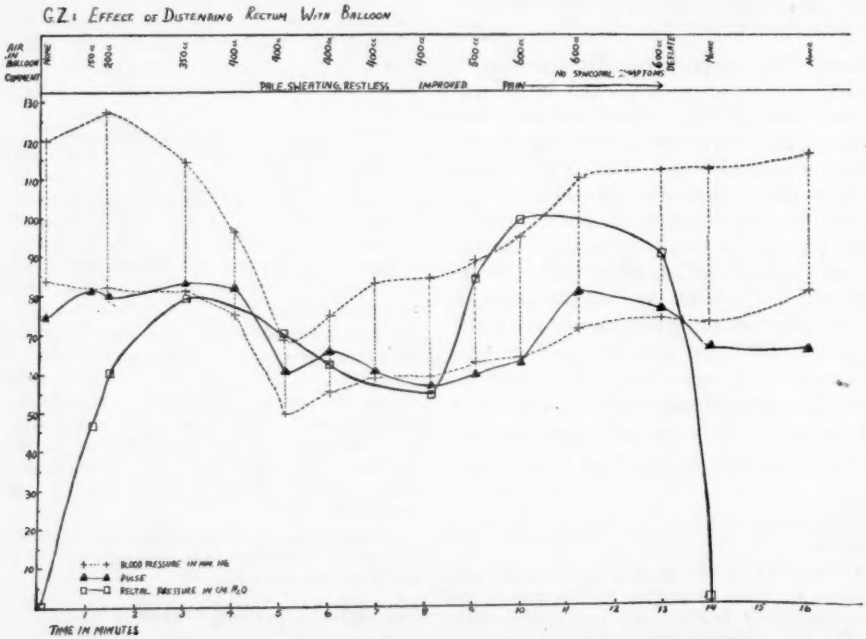

Fig. 4 (case 4).—The effect of pain on vasodepressor syncope produced by inflating a balloon in the rectum. Syncopal symptoms and fall in blood pressure resulted when the pressure within the balloon rose to 80 cm. of water. When pain was provoked by further inflation of the balloon, the blood pressure and pulse rate rose and symptoms disappeared.

Examination revealed a well developed and nourished man who belched frequently. No abnormalities were found in the cardiovascular system, the abdomen or the central nervous system.

The blood and urine were normal, and lumbar puncture revealed normal dynamics and normal fluid.

Roentgen examination of the skull revealed no abnormality. Serial roentgenograms of the gallbladder showed good visualization, and serial roentgenograms of the upper part of the gastrointestinal tract showed a normal esophagus, stomach and duodenal bulb. There was no hiatus hernia.

The electrocardiogram was normal.

Experiment (fig. 5).—The patient was studied seated in bed. A Levine tube with a small thin rubber balloon fastened to the tip was passed into the duodenum under fluoroscopic control.

profound collapse, with restlessness, pallor, profuse sweating, feeble, slow pulse (rate 45) and low blood pressure (50 mm. systolic and 30 diastolic). The electroencephalogram returned to the presyncope status, but ventricular escape and clinical collapse persisted for nine minutes, even with the patient recumbent. Then, immediately after the ballon was removed, sinus rhythm returned and clinical improvement began. After four minutes the blood pressure was 85 mm. systolic and 50 diastolic (with the patient recumbent) and the pulse rate was 60. The electroencephalogram was then normal.

Comment.—Although the data for blood pressure are incomplete, the symptoms and signs preceding actual loss of consciousness make it

likely that in this patient the reaction was primarily of vasodepressor origin, rather than due directly to sinus arrest. The subsequent prolonged depressor reaction tends to confirm this view. It is of great interest that the reaction was sustained as long as the offending balloon remained in place, even though it was no longer inflated, but that as soon as it was withdrawn sinus rhythm returned. In this instance the reaction was of such intensity that hypertension and

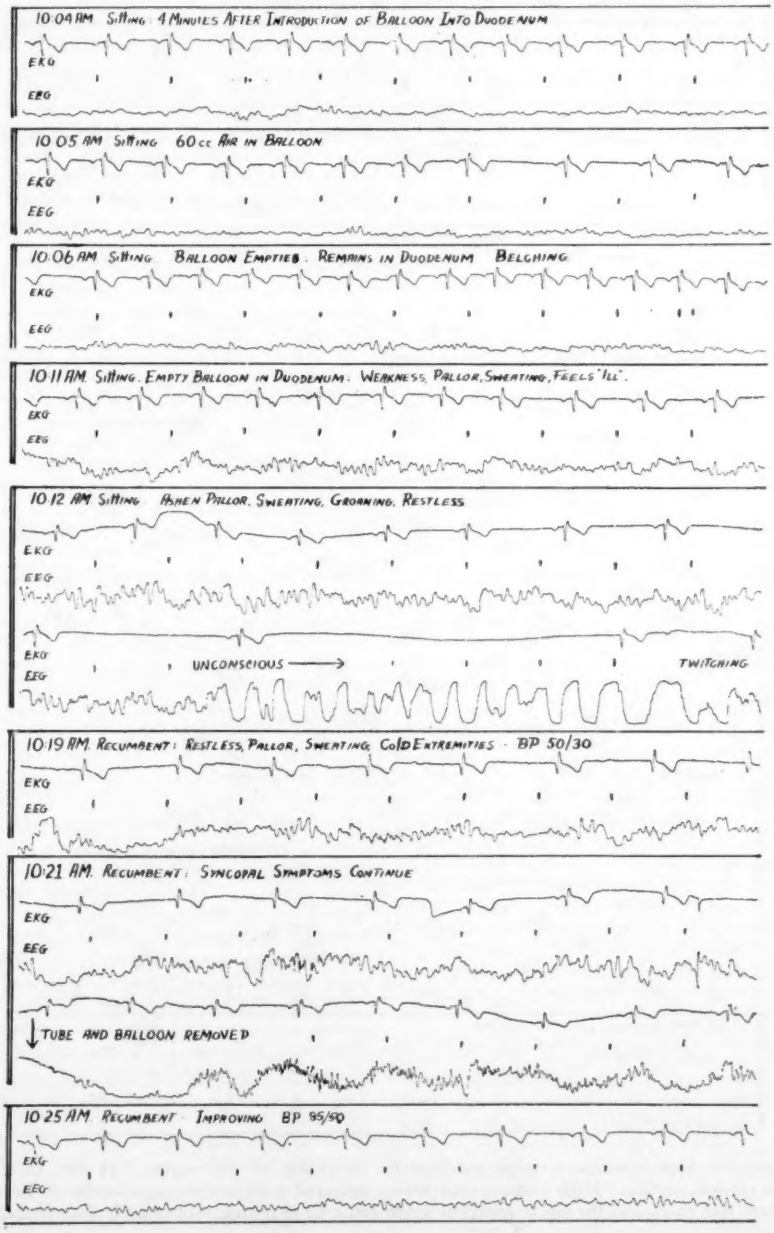

Fig. 5 (case 5).—Vasodepressor syncope provoked by distention of the duodenum. (The electrocardiographic leads are reversed.) Syncope was accompanied by lengthening sinus pauses and eventually by ventricular escape which lasted as long as the balloon remained in situ even though it was deflated. High voltage slow waves in the electroencephalogram appeared simultaneously with complete loss of consciousness and disappeared with return of consciousness, even though the other syncopal symptoms persisted for some time.

clinical symptoms persisted even when the subject was recumbent. However, consciousness was regained and the electroencephalogram returned to normal in spite of the other symptoms of collapse.

intestinal disturbance, possibly in the second or third portion of the duodenum; hence the duodenum was chosen for this experiment. After the duodenum had been intubated the symptoms of distress in the left upper quadrant

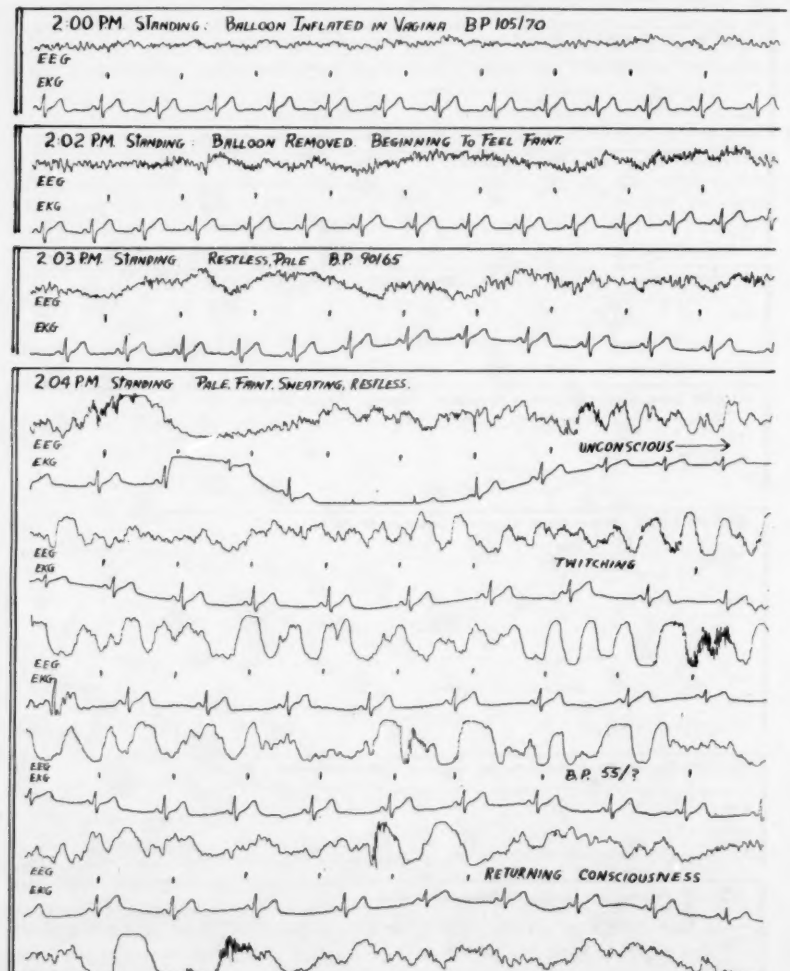

Fig. 6 (case 6).—Vasodepressor syncope provoked by distention of the vagina. In this case there was no disturbance in cardiac rhythm. High voltage slow waves appeared with loss of consciousness. Recovery occurred while the patient was erect, and the electroencephalogram returned to normal more slowly than in the previous cases.

The diagnosis in this case was not definitely established. From the clinical evidence it was thought that the patient had experienced spontaneous syncope provoked by some gastro-

disappeared and did not return. Inflation of the rectum, colon, esophagus and stomach on later dates did not provoke syncope. Three and four weeks later the experimental duodenal dis-

tention was repeated. On the first occasion the patient showed only occasional sinus pauses without symptoms; on the second occasion the blood pressure fell from 104 mm. systolic and 68 diastolic to 82 systolic and 75 diastolic, with early syncopal symptoms and belching, but recovery occurred when pain was produced by the introduction of more air. Because of these data it is not possible to state that the mechanism of spontaneous syncopal reactions in this patient had been demonstrated by the studies.

CASE 6.—*Syncope Provoked by Vaginal Distention.*

Clinical Data.—B. C., a 24 year old married woman, was referred for study because of fainting during a vaginal examination. Menses had begun at the age of 12 and had always been accompanied by spasmodic, colicky pain lasting about four hours. These symptoms frequently provoked syncopal symptoms, and the patient had fainted about four times a year for the past twelve years. Fainting during menstruation never occurred while the patient was recumbent. She had fainted also during incision of a boil and once after a severe sunburn. During her first year of marriage she had experienced considerable dyspareunia, but she had never fainted during coitus. Because of these symptoms the patient consulted Dr. Carl Walter, who performed a vaginal examination. While the patient was recumbent on the examining table with a speculum inserted in the vagina, pressure in the right fornix with an applicator produced pain; the patient became extremely pale, and the pulse could not be felt for several minutes.

Experiment (fig. 6).—The postural reactions, electroencephalogram and electrocardiogram were normal. A small soft rubber balloon at the end of a Levine tube was inserted into the vagina, and the patient was tilted to the erect position. The blood pressure was 105 mm. systolic and 70 diastolic. The balloon was inflated by hand with a rubber bulb. After two minutes the patient began to complain of faintness and the balloon was expelled. One minute later the blood pressure was 90 mm. systolic and 65 diastolic and weakness, faintness, pallor, sweating and restlessness progressed rapidly, leading to unconsciousness followed by twitching of the extremities. The systolic blood pressure was 55 mm. and the diastolic could not be determined. Unconsciousness was accompanied by high voltage slow waves as in previous experiments. The pulse rate slowed to 54, but there was no change in rhythm. The patient remained standing and after fifty seconds flushed and recovered consciousness, although her systolic blood pressure was only 60 and the diastolic still could not be determined. The electroencephalogram showed an irregular pattern of low voltage rapid waves before returning to normal. Two minutes later, with the patient in the recumbent position, recovery was complete.

Comment.—This case is another example of typical vasodepressor syncope. In this instance unconsciousness was not preceded by asystole, which demonstrates that this is not an essential phase of vasodepressor syncope. As in case 1, the subject recovered consciousness before being lowered. However, recovery was slower, and there was a longer interval before the electroencephalogram returned to normal.

SYNCOPE FOLLOWING HYPERVENTILATION

Vigorous hyperventilation for three minutes normally provokes numbness, tingling, lightheadedness, buzzing in the head, and varying degrees of disturbance in consciousness. When tested psychologically most subjects are found to have disturbed awareness at the height of the reaction and to have retrograde amnesia for this period. This is the point of maximum electroencephalographic change, and both slowing of the brain waves and disturbance in awareness are more evident when the patient is erect than when he is recumbent.[6] It is unusual, however, to see true syncope in which the period of diminished consciousness is accompanied also by loss of muscle tone and falling. Occasionally, however, hyperventilation will initiate a vasodepressor reaction. We have observed syncope of this type only twice in examination of a large series of subjects during hyperventilation on the tilt table.

CASE 7.—*Clinical Data.*—R. G., a 19 year old youth, entered the Peter Bent Brigham Hospital for the study of convulsive seizures which had begun eighteen months earlier. These attacks were characterized by loss of consciousness, staring and tonic and clonic movements of the extremities. They were occasionally preceded by a cry and were usually followed by confusion. On one occasion the patient bit his tongue.

The history and results of examination appeared to justify the diagnosis of epilepsy.

Experiment (fig. 7).—The resting electroencephalogram was normal, with a well developed alpha frequency of 8 to 10 cycles per second and no evidence of any focal disturbance.

The patient was tilted to the erect position, and after eleven minutes the blood pressure was unchanged (110 mm. systolic and 80 diastolic). He was then instructed to hyperventilate vigorously for three minutes. The electroencephalogram showed increase in voltage and slowing to 5 or 6 cycles per second at the end of one hundred and fifty seconds. (The maximum change is illustrated in figure 7.) His blood pressure at the end of the period of hyperventilation was 92 mm. systolic and 75 diastolic. He experienced numbness and tingling of the hands and some fulness in the head during the hyperventilation. The electroencephalogram returned to normal. Two minutes later the patient began to feel weak, faint and nauseated, and sweating and pallor appeared. He lost consciousness and slumped; simultaneously high voltage slow waves (2 to 4 per second) appeared in the electroencephalogram. There was no significant change in the rate or the rhythm of the heart. After thirty seconds, while still erect, the patient sighed, and recovery began. The frequency of the brain waves increased quickly to 6 to 7 per second, but before becoming normal the encephalogram showed a low voltage fast stage. Two minutes after recovery

6. Engel, G. L.; Romano, J.; Ferris, E. B., Jr.; Webb, J. P., and Stevens, C. D.: A Simple Method of Determining Frequency Spectra in the Electroencephalogram: Observations on Physiological Variations in Glucose, Oxygen, Posture, and Acid-Base Balance on the Normal Electroencephalogram, Arch. Neurol. & Psychiat. **51**:341 (April) 1944.

began the blood pressure was 60 mm. systolic and 50 diastolic and the patient was extremely pale and was sweating. Two minutes later, when the electroencephalogram was again normal, the blood pressure was 80 mm. systolic and 60 diastolic.

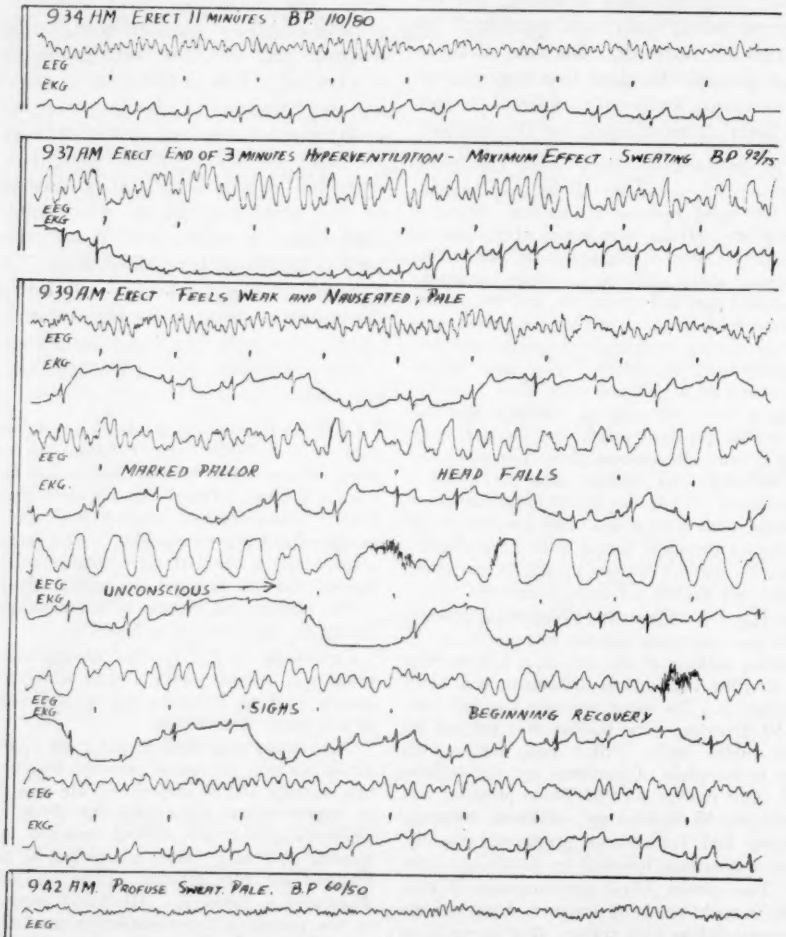

Fig. 7 (case 7).—Vasodepressor syncope provoked by hyperventilation. The maximum electroencephalographic change accompanying hyperventilation is illustrated in the second strip. The electroencephalogram returned to normal while syncopal symptoms were developing, but high voltage slow waves appeared with loss of consciousness. The patient recovered consciousness while still erect, although the blood pressure was only 60 mm. systolic and 50 diastolic. The electroencephalogram passed through a stage of low voltage fast activity before normal alpha rhythm returned. There was no convulsion.

Comment.—The reaction described is again typical vasodepressor syncope. Because hyperventilation so rarely results in a serious fall in blood pressure which persists or progresses after hyperventilation has been discontinued, it does not seem reasonable to ascribe this reaction to a direct effect of the hyperventilation alone on the circulatory dynamics. An additional and perhaps more important factor may be the psychologic reaction to the unexpected symptoms of numbness, tingling and lightheadedness experienced during hyperventilation. The sense of

impending unconsciousness, which is subjectively not dissimilar to that experienced during induction of anesthesia, is frightening to some persons and represents a threatening situation, which may play a role in the initiation of any vasodepressor reaction. The occurrence of vasodepressor syncope merely at the sight of blood or of mutilation has already been commented on.

The electroencephalographic changes in this case are of some interest. The hyperventilation effect had completely disappeared before the syncopal reaction had reached its peak. Recovery occurred while the patient was erect, this time without any convulsive movements. In contrast to the quick return to normal when a subject is lowered, the recovery was slow; the electroencephalogram passed through a phase of slow activity (4 to 7 cycles per second) and then through one of low voltage fast activity before returning to normal. This progression of changes during recovery is similar to that described during recovery from delirium, except that the latter requires days or weeks.[7] A similar, though less striking, progression of changes is visible in the record of the other subject whose recovery was delayed by the patient's remaining in the erect position (case 8).

It is noteworthy that this boy who undoubtedly had clinical epilepsy (in spite of the normal electroencephalogram) experienced unconsciousness due to diminished cerebral blood flow and yet did not have an epileptic seizure. The combination of factors necessary to provoke a seizure in a person with epilepsy is obviously more complex.

CASE 8.—*Clinical Data.*—L. W., an 18 year old college girl, came to the Peter Bent Brigham Hospital for study of fainting attacks of one year's duration.[8] These attacks had always occurred while the patient was in the upright position and usually after she had been standing for some time, as in the church choir. They were characterized by progressive weakness, faintness, pallor, sweating, blurring of vision and finally falling with loss of consciousness. She recovered consciousness rather promptly in the recumbent position, although weakness and unsteadiness persisted for thirty minutes or more.

Examination revealed a tall, thin girl with cold hands and feet, but there were no other abnormal physical signs.

Experiment.—While the patient was recumbent her pulse rate was 66 to 72, with moderate sinus arrhythmia; the blood pressure was 110 mm. systolic and 80 diastolic; the electrocardiogram was normal and the electroencephalogram was normal with a predominant pattern of low voltage, fast waves and poorly developed alpha waves. The patient was tilted up 75 degrees on the tilt table. The pulse rate increased at once to 108 and in eleven minutes to 138. The pulse pressure progressively decreased as the patient stood and in fifteen minutes it was only 14 (systolic blood pressure 100, diastolic 86). At that point the patient was instructed to hyperventilate. The pulse rate promptly increased to 162, while the systolic blood pressure dropped to 60 mm. and the diastolic could not be recorded. In thirty-five seconds, before any significant slowing of the brain waves had occurred, there was an abrupt sinus arrest with ventricular escape and loss of consciousness; high voltage, 2 to 3 per second waves appeared in the electroencephalogram. The patient was lowered, and consciousness returned, but not before transient twitching of the upper extremities had developed. The electroencephalographic electrodes were broken during the faint; hence only a ten second record was obtained during the syncopal reaction.

Comment.—This case illustrates a second mechanism whereby hyperventilation may provoke syncope. The patient had poor postural adaptation; this was suggested by the history of the spontaneous attacks and shown by the acceleration of the heart rate and the decrease in the pulse pressure when she stood. Although the changes in the pulse and blood pressure had slowly progressed, at the end of the fifteen minutes' standing there was still no clincial evidence of impending syncope. After thirty-five seconds of hyperventilation, however, syncope occurred abruptly. Hyperventilation normally causes increase in heart rate and some decrease in pulse pressure, but in this case the changes rapidly exceeded the limits compatible with consciousness. Syncope probably would have occurred in the absence of hyperventilation, but the latter certainly appeared to accelerate the reaction.

VASODEPRESSOR SYNCOPE PROVOKED BY STIMULATION OF THE CAROTID SINUS

Pure vasodepressor syncope without significant bradycardia, which can be regularly provoked by massage of the carotid sinus, is of rare occurrence. We have encountered only one example in more than 60 persons with hypersensitivity of the carotid sinus reflex. Some data on this case have already been reported in another paper.[4c] The patient was a 59 year old man who had had attacks of dizziness and lightheadedness for five years and for two years had had attacks of unconsciousness in which he would fall to the ground. The patient himself had discovered that the attacks seemed to be precipitated by turning the head, by wearing tight collars and by bending forward. He had

7. Romano, J., and Engel, G. L.: Delirium: I. Electroencephalographic Data, Arch. Neurol. & Psychiat. **51**:356 (April) 1944. Engel, G. L. and Romano, J.: Delirium: II. Reversibility of the Electroencephalogram with Experimental Procedures, ibid. **51**:378 (April) 1944.

8. This patient was referred to us by Dr. Eugene A. Stead Jr.

as many as ten attacks a day unless he carefully avoided such activities.

Experiment.—Postural reactions on the tilt table were normal. When the patient was erect, massage of the right carotid sinus regularly produced, within thirty seconds, pallor, hyperpnea, dizziness and finally unconsciousness with falling. Clonic twitching occurred if the reaction was sustained. The reaction was accompanied by slowing of the pulse rate from 80 to 50 or 60, without asystole, and by a rapid fall in the blood pressure to levels which could not be measured by auscultatory methods. When massage of the carotid sinus was discontinued, there was flushing of the face followed by rapid return of consciousness. When the patient was in the recumbent position, the systolic blood pressure fell to 60 mm. or lower but unconsciousness did not occur. Fall in blood pressure and syncope were not prevented by subcutaneous administration of 1/25 grain (2.4 mg.) of atropine sulfate, though it resulted in an increase in pulse rate to 116 and abolished the slight slowing of the heart which usually occurred when the carotid sinus was massaged. Ephedrine, epinephrine, paredrinol sulfate (α-n-dimethyl-p-hydroxyphenylethylamine), paredrine hydrobromide (p-hydroxy-α-methylphenylethylamine hydrobromide) and amphetamine sulfate administered parenterally in doses sufficient to cause a significant rise in arterial blood pressure failed to prevent the depressor reaction when the patient was erect, though they diminished it when the patient was recumbent. Desoxycorticosterone acetate (10 mg. daily, intramuscularly) and sodium chloride administered for five days were also without effect. The electroencephalogram during syncope was characterized by high voltage slow waves (3 to 6 per second) which were not localized.

Comment.—Of interest in this case is the fact that vasopressor drugs were ineffective in preventing a reflex fall in blood pressure when the patient was erect. All these drugs act primarily on arterioles, although Kunkel, Stead and Weiss[9] have suggested that paredrinol sulfate may in addition increase venous tone. Paredrinol sulfate, indeed, was the most effective drug in the group. Additional evidence that reflex vasodepressor reaction of this type is not incompatible with maximum arteriolar constriction produced by epinephrine was shown by observation of a patient with pheochromocytoma of the adrenal medulla[10]; during a paroxysm of hypertension in which the blood pressure was 310 mm. systolic and 170 diastolic massage of the right carotid sinus led to a prompt fall in the blood pressure to 160 mm. systolic and 115 diastolic, with only slight slowing of the pulse and with immediate return to the previous level when the stimulation was discontinued. Chu and Hsu[11] have shown in animals that epinephrine increases the sensitivity of the blood pressure–regulating mechanism of the carotid sinus to the existing pressure.

SYNCOPE ASSOCIATED WITH HYPERSENSITIVITY OF THE CAROTID SINUS REFLEX

Because Forster, Roseman and Gibbs[4e] recently stated that slow waves of cortical origin are rare in electroencephalograms made during carotid sinus syncope, it seems important to add to the observations reported by one of us in 1941 and 1942.[4b, c] The electroencephalographic data for 7 cases of carotid sinus hypersensitivity of the cardioinhibitory type, 1 of the depressor type and 7 of the cerebral type were reported. In all instances unconsciousness was accompanied by the appearance in the electroencephalogram of slow waves (3 to 6 per second) of moderate to high voltage, which were sometimes followed by a period of random low voltage activity. The degree of change in the electroencephalogram was directly related to the intensity and duration of the disturbance in consciousness. There was no significant difference in the character of the electroencephalographic changes in the three types of hypersensitivity of the carotid sinus reflex.

Six new cases of hypersensitivity of the cardioinhibitory type and 3 new cases of hypersensitivity of the cerebral type have been studied.

The typical electroencephalographic changes in cardioinhibitory carotid sinus syncope are illustrated in figure 8. Moderate to high voltage slow (3 to 6 per second) waves always appeared if consciousness was lost, and they occurred simultaneously with the loss of consciousness. Loss of consciousness was most readily provoked when the subjects were standing; the advent of unconsciousness was heralded by muscular relaxation and slumping, and the subjects were prevented from falling only by the restraining straps. When only lightheadedness or giddiness was experienced, the electroencephalographic changes were likely to be less striking and included chiefly decrease in the amplitude and in the amount of alpha activity, with minimal amounts of slow activity. Such a reaction is illustrated in figure 9. Clonic twitches frequently occurred when unconsciousness was unusually prolonged, but except for the occasional superimposition of muscle potentials, the electroencephalogram did not differ essentially from that recorded in the absence of muscular twitching. When the subject was in the recumbent position, even asystole of ten to fifteen sec-

9. Kunkel, P.; Stead, E. A., Jr., and Weiss, S.: Effect of Paredrinol (alpha-N-dimethyl-p-hydroxyphenethylamine) on Sodium Nitrite Collapse and on Clinical Shock, J. Clin. Investigation **18**:679, 1939.

10. Engel, F. L.; Mencher, W. H., and Engel, G. L.: "Epinephrine Shock" as a Manifestation of a Pheochromocytoma of the Adrenal Medulla, Am. J. M. Sc. **204**:649, 1942.

11. Chu, L. W., and Hsu, F. Y.: The Effect of Adrenaline on Vasomotor Reflexes, Quart. J. Exper Physiol. **27**:307, 1938.

onds did not usually lead to complete unconsciousness and there was little or no change in the electroencephalogram.

The cases of syncope due to carotid sinus sensitivity of the cerebral type included 1 in which complete loss of consciousness was followed by clonic twitching on the right side and 2 in which focal neurologic signs and symptoms occurred without serious disturbance in consciousness. In the first case unconsciousness was accompanied by the appearance of diffuse, somewhat irregular slow waves (3 to 6 per second) followed by random low voltage fast activity. The clonic twitches occurred in the latter phase of the reaction and introduced some muscle potentials into the record. This record is essentially the same as those reported for the 7 cases cited in earlier papers.[4b, c]

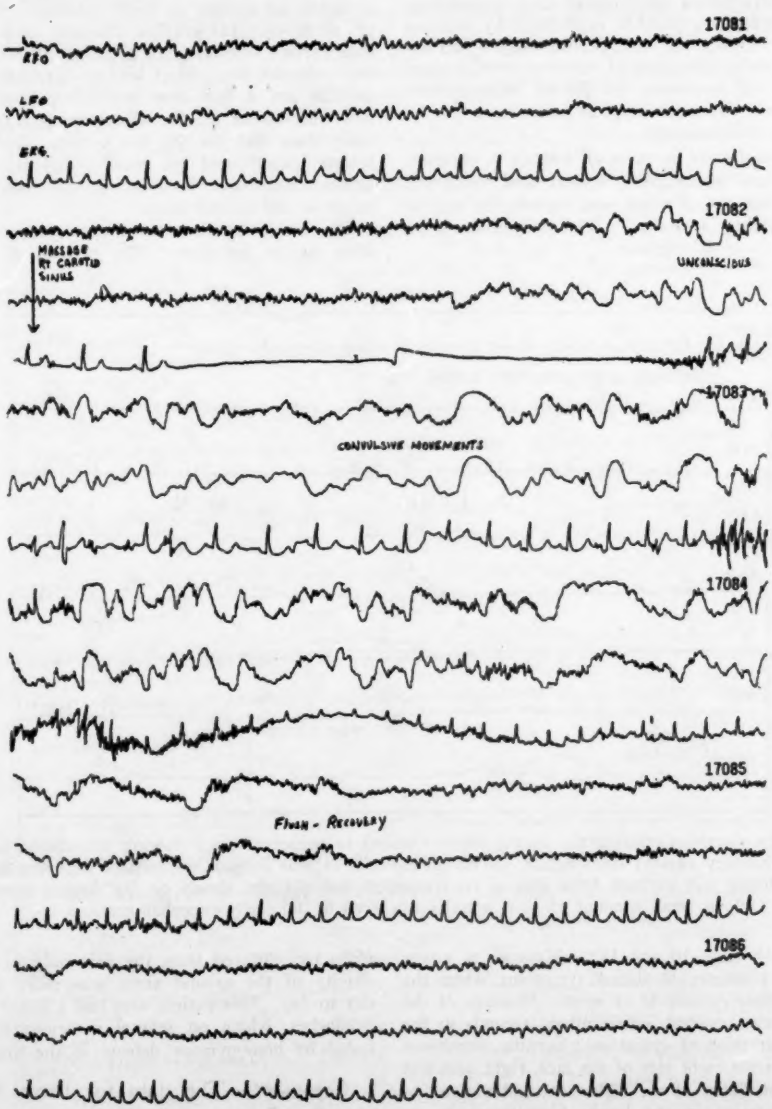

Fig. 8.—The electroencephalogram during unconsciousness following stimulation of a hypersensitive cardioinhibitory carotid sinus reflex. With an asystole of eight seconds there was complete loss of consciousness with falling, followed by clonic movements. The electroencephalogram showed high voltage slow waves during the period of unconsciousness.

The remaining 2 cases are of special interest, and 1 will be described in detail.

CASE 9.—*Clinical Data.*—G. E., a 28 year old physician, had experienced lightheadedness for at least

twenty years when he looked over either shoulder. This was particularly disturbing, for example, when he attempted to back a car out of a garage. The symptoms consisted chiefly of lightheadedness, buzzing in the head and numbness and tingling of the arm toward which he turned. At the age of 10 years, when a companion playfully threw a towel over his neck from behind and pulled on it momentarily, he lost consciousness. Two years before he consulted us it was discovered that the symptoms could be reproduced by pressure on the carotid sinuses. In addition, the subject had experienced the early symptoms of vasodepressor syncope on a number of occasions, as during venipuncture, arterial puncture or minor surgical procedures, but he had never lost consciousness.

There was no family or personal history of epilepsy. The patient had occasionally experienced unilateral frontal headaches, one of which was preceded by contralateral scintillating scotomas. The symptoms were thought to be those of migraine.

Stimulation of the right carotid sinus resulted in identical symptoms on the left side and electroencephalographic changes in the record of activity of the right cortex. After stimulation was discontinued, there was flushing of the face and prompt disappearance of both the symptoms and the electroencephalographic abnormalities.

As a control experiment each carotid artery was occluded for twenty to thirty seconds. No symptoms or electroencephalographic changes occurred. When both carotid arteries were occluded for ten seconds and then released, the subject became lightheaded for a few seconds and a few slow waves appeared which were more prominent in the electroencephalogram for the right than that for the left cortex. Subjectively the patient experienced no focal symptoms but a more serious disturbance in consciousness than from stimulation of the carotid sinus.

The results in the second case were essentially the same as in the first. The patient, a 36 year old

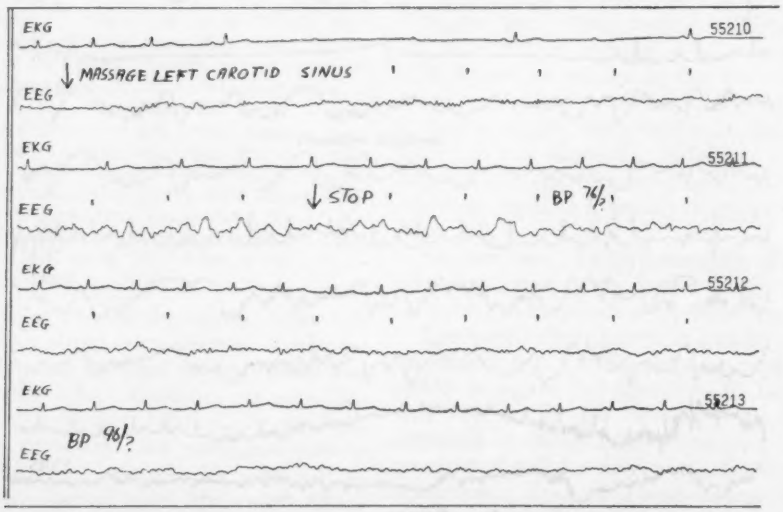

Fig. 9.—The electroencephalogram during minor changes in consciousness following stimulation of a hypersensitive cardioinhibitory carotid sinus reflex. With an asystole of four seconds the subject experienced lightheadedness and giddiness and perhaps brief loss of consciousness but did not slump or fall before stimulation was discontinued. Only a small amount of slow activity appeared in the electroencephalogram.

Experiment[12] (figs 10 and 11).—Massage of either carotid sinus promptly produced symptoms when the patient was either recumbent or erect. Massage of the left carotid sinus resulted within fifteen seconds in the following progression of symptoms: burning, numbness and tingling of the right side of the face, right arm and right leg, clonic jerks of the right arm and a sense of fulness and buzzing in the head. Simultaneously, in the electroencephalogram high voltage, irregular, slow waves (2 to 5 per second) appeared from the cortex on the left side (fronto-occipital lead), while the cortex on the right side showed no slowing of activity, only a slight decrease in regularity.[13] There was no change in the pulse or the blood pressure during this reaction.

12. Dr. Eugene B. Ferris, Jr., aided in these observations.

13. More complete studies of localization will be reported at a later date.

physician, differed from the first only in that the sensitivity of the carotid sinus was more variable from day to day. This patient also had a history of migraine headaches, which on several occasions had been preceded by homonymous defects in the visual fields.

Comment.—The data for these 3 cases and for the 7 cases previously reported indicate that, contrary to the findings of Forster, Roseman and Gibbs,[46] slow waves of cortical origin are a prominent feature in carotid sinus syncope of the cerebral type and, further, that when focal neurologic signs and symptoms occur without loss of consciousness they are associated with slow waves which arise from the corresponding hemisphere. When unconsciousness occurs, the slow waves arise diffusely and subsequent focal

manifestations do not lead to any further change. Abnormally slow waves arising from one cortex might result either from a local reflex vasoconstriction or from a direct cortical reflex mediated through the midbrain. The observations of Ferris, Capps and Weiss[1] that some cerebral vasoconstriction takes place during syncope of this type would favor the former explanation, in spite of the fact that these investigators found no change in total cerebral blood flow. Restriction of flow through a local cortical area may well take place without being of such magnitude as to be reflected in measurements of total cerebral flow.

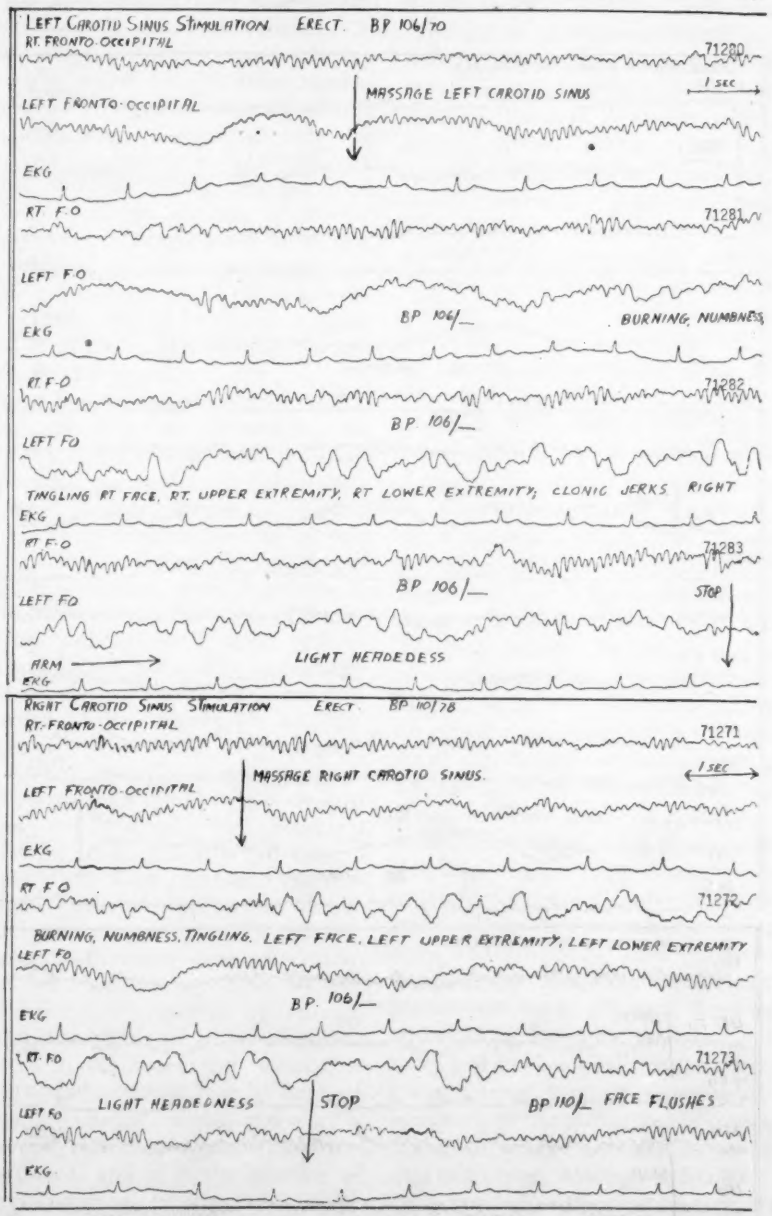

Fig. 10 (case 9).—Electroencephalographic changes during cerebral type of carotid sinus syncope, with focal changes. The abnormal cortical potentials appeared on the side corresponding to the stimulated carotid sinus, while sensory and motor symptoms developed contralaterally.

COMMENT

ELECTROENCEPHALOGRAPHIC DATA

In every case of syncope reported in this paper and in the earlier papers, slow waves invariably appeared in the electroencephalogram when the reaction was allowed to progress to the stage of complete unconsciousness. The criteria for complete unconsciousness were loss of control of the voluntary muscles, evidenced by falling of the head on the chest, buckling of the knees and slumping in the restraints, and lack of response

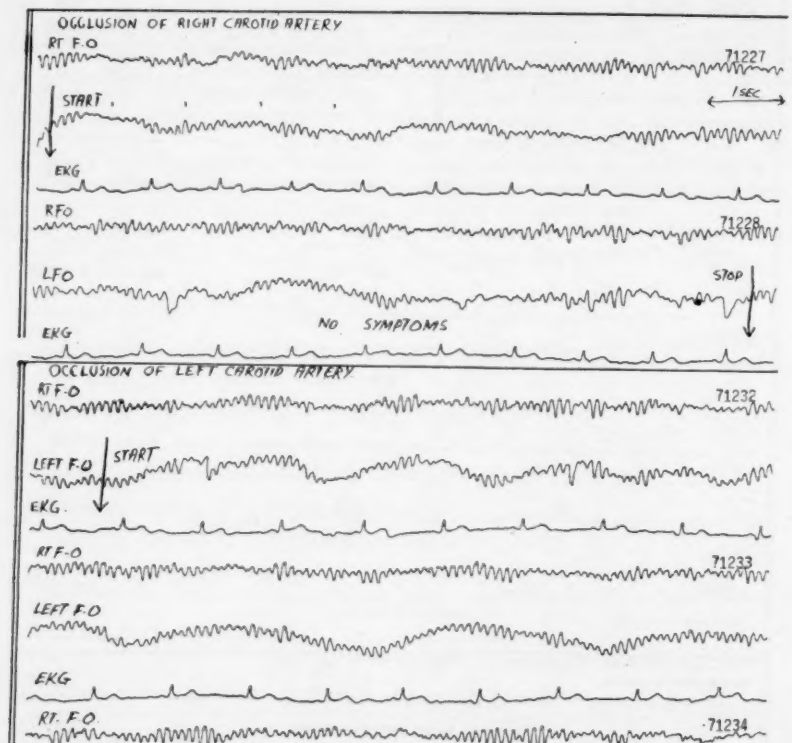

Fig. 11 (case 9).—Effect of occlusion of the carotid artery on carotid sinus syncope of the cerebral type. Occlusion of each artery separately for twenty to thirty seconds was without effect. Occlusion of both arteries for ten seconds produced some lightheadedness and some slow activity in the electroencephalogram, most evident on the right side.

to stimuli; usually there was retrograde amnesia. When recovery from complete unconsciousness was delayed by keeping the subject in the erect posture, the return of the electroencephalogram to normal passed through the following stages: (1) decreased amplitude of slow waves, with frequency increasing to 4 to 6 per second, (2) random low voltage fast activity and (3) low amplitude regular waves which rapidly reached alpha frequency (8 to 12 per second). As already mentioned, these stages, occurring over the course of seconds or minutes, are essentially the same as those observed during recovery from delirium over the course of days or weeks.[7] Clinically subjects recovering slowly from syncope show evidence of confusion during the period preceding the return of the electroencephalogram to normal. When recovery is rapid, it is not possible to distinguish successive stages in the electroencephalogram.

In contrast to the striking slowing of cortical waves during complete unconsciousness, the changes during the lesser degrees of disturbed consciousness, such as giddiness, lightheadedness, roaring in the head, confusion and blurring of vision, and during unconsciousness of only one or two seconds' duration are much less apparent. Such symptoms were found to be associated with no change, with waves of diminished amplitude, with decreased alpha activity, with varying amounts of low voltage fast activity or with small amounts of low to moderate voltage slow activity (4 to 7 cycles per second). These changes, it will be noted, are essentially the same, in reverse order, as those noted during delayed recovery from complete unconsciousness, and in our opinion they represent intermediate stages, both clinically and electroencephalographically. They represent quantitative rather than qualitative differences in the electrical activity of the cortex. The electroencephalographic differences between orthostatic syncope (or vasodepressor syncope) and carotid sinus syncope, as reported by Forster, Roseman and Gibbs, [4e] result in all likelihood from differences in the speed with which the two types of syncopal reactions may be initiated and terminated. Carotid sinus syncope is ordinarily promptly terminated when the stimulus is discontinued, and it is the practice of most examiners to discontinue stimulation at the first evidence of a reaction. Orthostatic (or vasodepressor) syncope, on the other hand, can be reversed only by tilting the subject back to the recumbent position, and the time necessary for this maneuver is usually long enough that the reaction can go on to the phase of complete unconsciousness.

Actually the data of Forster, Roseman and Gibbs are entirely consistent with ours. In their illustrated example of cardiodepressor carotid sinus syncope (Forster, Roseman and Gibbs [4e] fig. 1) the duration of asystole was only four and a half seconds, which in our experience is not sufficient to produce more than fleeting unconsciousness when the patient is seated. The exact duration of unconsciousness is difficult to determine, particularly when the patient's eyes are closed. When loss of consciousness is prolonged, the subject often opens the eyes on recovery, owing to transient amnesia for the earlier request to keep them closed. This apparently did not occur in the example illustrated. In their second example (Forster, Roseman and Gibbs,[4e] (fig. 2), in which slow waves did occur, the asystole lasted six seconds and was followed by idioventricular rhythm, with the pulse rate 40, which suggests either that stimulation was continued throughout or that there was a strong vasodepressor reaction. (Blood pressures are not shown.) These figures may be compared with the illustrations in this report of asystole of eight seconds (fig. 8) and asystole of four seconds (fig. 9), both in standing subjects. The magnitude of the electroencephalographic changes is much greater in the first of these, in which asystole was longer and unconsciousness more sustained. Similarly, the lack of significant electroencephalographic changes in vasodepressor syncope in which the subject experienced lightheadedness and blurring of vision but not complete loss of consciousness is illustrated in figure 2 of this report.

In carotid sinus syncope of the cerebral type the same reactions were noted. Diffuse slow activity accompanied sustained unconsciousness, and focal slow activity accompanied focal cortical signs and symptoms when the latter were not preceded by complete unconsciousness. The patient reported by Romano, Stead and Taylor [4d] and cited by Forster [4e] as showing only fast activity and no slow waves on the electroencephalogram during syncope experienced subjective symptoms of impending loss of consciousness but did not experience sustained unconscousness. The data of Forster, Roseman and Gibbs [4e] on carotid sinus syncope of the cerebral type are also open to criticism on the grounds that the specificity of the carotid sinus as the sensitive zone was not established. Many patients with hysterical fainting will faint on manipulation of many areas of the body, including the neck. Recent studies have demonstrated that hysterical fainting is marked by the absence of changes in the brain

waves even during prolonged unconsciousness. These observations will be the subject of another report.[14]

MECHANISM OF VASODEPRESSOR SYNCOPE

A number of points concerning vasodepressor syncope have been brought out by these studies and may be summarized as follows:

1. Vasodepressor syncope may be provoked by a variety of sensory stimuli. The meaning to the subject and the setting of the sensory stimulus seem to be more important than the specific nature of the sensory modality. Thus pain may provoke or prevent vasodepressor syncope under different circumstances. Nor does the sensory stimulus bear a simple direct relationship to the reaction, since it was usually not possible to provoke syncope in the same subject on repeated occasions by the same stimulus. This suggests that other factors are involved. Since it is well known that vasodepressor syncope may be provoked by purely psychologic experiences, for example, viewing mutilation, seeing blood or hearing bad news, it is likely that emotional reactions to threatening and unusual situations play a potent role in precipitating vasodepressor syncope. This relationship probably explains "first experience" syncope and indicates that learning plays an important role in the conditioning process.

2. The vasodepressor reaction may continue for a considerable period after the original stimulus has been withdrawn. In effect, the disturbance in the circulatory apparatus results in a discrepancy between the volume of the vascular bed and the volume of circulating blood. In most instances of vasodepressor syncope this discrepancy can be overcome by eliminating the effects of gravity in pooling blood in dependent portions of the body. It was not established in these studies whether the deleterious effects of erect posture indicated that the normal postural reflexes involved in returning blood to the right side of the heart were absent or merely inadequate under the circumstances.

3. Most of the symptoms and signs of vasodepressor syncope, such as pallor, sweating, weakness, nausea and faintness, are secondary to the falling arterial blood pressure. This was shown by the prompt improvement in the recumbent position when the blood pressure rose, even though the persistence of the fundamental disturbance could be repeatedly demonstrated by returning the subject to the erect posture. When the disturbance was severe and the blood pressure remained low even when the patient was in the recumbent position (as in case 5), symptoms persisted as long as the hypotension was present. At what point such a condition passes into what is described by some as "primary shock" would be difficult to say.

4. Unconsciousness is a late phenomenon, occurring only when the arterial blood pressure or the pulse pressure has reached extremely low levels. The term "syncope" should not be restricted to those instances in which complete unconsciousness occurs but properly includes the entire reaction preceding unconsciousness. When unconsciousness supervenes, several events take place which may lead to recovery even when the patient is erect. The advantage of falling is obvious. The factors leading to recovery while the patient is still erect may include cerebral reflexes secondary to cerebral hypoxia and the mechanical and reflex effects of convulsive movements. In 1 of our cases the latter effects did not occur. Convulsive movements are apparently not essential to recovery. Soma Weiss[15] has discussed "irreversible syncope" as a cause of sudden death. One wonders whether some such cases are not instances in which these emergency mechanisms are not effectively evoked.

5. Although recovery does occur in the erect position, it is obviously much safer to place the subject experiencing syncopal symptoms in the recumbent position. However, once it is apparent that the provoking stimulus is no longer active, prolonged motionless recumbency will frequently prolong the reaction. The patient should be encouraged to move about, flexing and extending the legs, and should be gradually restored to the erect position but warned against motionless standing or even sitting. The time-honored remedies of slapping the face, splashing it with cold water and administering smelling salts have a sound theoretic basis as means of stimulating muscular activity (resistance) and increasing sympathetic activity.

SUMMARY

Vasodepressor syncope was provoked in 9 patients by venipuncture, by distention of the rectum, colon, duodenum or vagina, by hyperventilation or by stimulation of the carotid sinus. In addition, 6 cases of the cardioinhibitory type of carotid sinus syncope and 3 cases of the cerebral type were studied.

Complete unconsciousness, characterized by unawareness, muscular relaxation and falling,

14. Romano, J., and Engel, G. L.: Studies of Syncope: III. Differentiation Between Vasodepressor Syncope and Hysterical Fainting; to be published.

15. Weiss, S.: Instantaneous "Physiologic" Death, New England J. Med. **223**:793, 1940.

was always accompanied by high voltage slow waves in the electroencephalogram, regardless of the mechanism by which unconsciousness was provoked. Lesser changes in consciousness, such as lightheadedness, giddiness and transient unconsciousness, were associated with less obvious slowing of the electroencephalogram, loss of alpha activity or no change at all. In 2 cases of the cerebral type of carotid sinus syncope the development of contralateral focal neurologic signs and symptoms without loss of consciousness was associated with abnormal waves from the ipsilateral cortex.

Vasodepressor syncope could be provoked by a wide variety of sensory stimuli, but the significance of the stimulus to the subject seemed to be more important than the specific modality involved. Most of the symptoms of vasodepressor syncope were associated with falling arterial blood pressure, and unconsciousness did not develop until blood pressure had fallen to a low level. Symptoms could be relieved by returning the subject to the recumbent position, but they often recurred if the subject stood up again, even if the original stimulus had been withdrawn. The derangement in circulatory dynamics was apparently compensated for but not corrected by assumption of the recumbent position, presumably by avoiding the pooling effects of gravity. Recovery of consciousness may occur in the erect position; convulsive movements and increase in muscle tone seemed to aid recovery, but they were not essential. The value of having the patient exercise before standing up was evident.

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INTESTINAL MALABSORPTION ASSOCIATED WITH TUBERCULOSIS OF MESENTERIC LYMPH NODES

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The symptomatic manifestations of tuberculosis may be almost as varied as those of syphilis. However, since the course in adults is manifested usually as one of the two or three most common types, clinicians tend to overlook some of the more unusual manifestations. It is the purpose of this report to present studies on a case of intestinal malabsorption associated with tuberculosis of the mesenteric and retroperitoneal lymph nodes, carried out over a period of four years.

REPORT OF A CASE

A 16 year old white school boy was first seen by one of us (W. B. P.) on Jan. 9, 1935, complaining of diarrhea. Two years previously diarrhea began insidiously, with four to eight watery stools daily; no other associated symptoms were noted. Examination of his stools at that time revealed the dwarf tapeworm. During the two subsequent years he received several types of medication without improvement; the symptoms became more severe and the tapeworm remained present in the stools. During the five months preceding his first visit symptoms were greatly aggravated, stools approaching eight or ten a day. Edema of the legs and face appeared and persisted until he was seen. Soreness of the tongue also became noticeable. Tonsillectomy had been performed when he was 2 years old. He had had the usual diseases of childhood, scarlet fever and "rheumatism." His childhood was spent on a farm, where he was fed raw milk from a cow which was subsequently found tuberculous and destroyed. There was no family history of tuberculosis.

On physical examination he appeared healthy, and the general examination revealed nothing abnormal except some abdominal distention and tenderness over the left lower quadrant. There was slight dependent edema. Sigmoidoscopic examination revealed no abnormalities of the rectum or lower part of the sigmoid colon. He was placed on a high protein diet and given dilute hydrochloric acid and liver extract[1] orally. On this regimen, with added symptomatic treatment for the diarrhea, he improved slightly during the next two months. On Feb. 27, 1939, since his basal metabolic rate was —27 per cent, thyroid was given. On April 25 signs and symptoms indicating acute appendicitis appeared; operation was performed and a gangrenous appendix removed. The patient recovered uneventfully from this episode, and healing of the wound was rapid despite the abnormalities of blood chemistry (table 6). After the operation all his former symptoms reappeared, with the recurrence of considerable edema and severe diarrhea. The previous medications were resumed, with some subjective improvement but without any alteration of the blood chemistry. During the next year he was seen frequently; however, there was little change. On April 3, 1940 treatment against Hymenolepis nana was instituted. The edema and diarrhea continued from time to time. In August the patient suffered a brief acute illness characterized by chills, fever and severe herpes simplex; he recovered from this rapidly. On October 7 he first noted the phenomenon of tetany, with numbness and spasms of the hands and face; these symptoms had been preceded by an infection of the upper respiratory tract, with aggravation of the diarrhea. Tetany persisted thereafter, precipitated by exertion or increasing diarrhea.

On March 6, 1941, the patient was first admitted to the hospital for study. On examination, the temperature was 98.4 F., the pulse rate 80 and the respiratory rate 20; the blood pressure was 110 systolic and 80 diastolic. His complexion was pasty and the skin appeared thin and somewhat "transparent." The tongue was definitely reddened, but without papillary atrophy. There were a few slightly enlarged firm cervical lymph nodes. The heart was normal, and the lungs were clear. The abdomen was soft and flat and no masses were felt; the firm, smooth edge of the liver was palpable 3 cm. below the right costal border; rectal and neurologic examinations gave normal results. The Chvostek and Trousseau signs of tetany were present. The nails were ridged and brittle, and 2+ edema of both lower legs was present. In the hospital, at rest in bed and on the regular house diet, he had two or three watery stools a day but felt generally fairly well. On March 18 he was placed on a diet consisting of carbohydrate 270 Gm., protein 95 Gm. and fat 60 Gm. During this period the patient felt better than ever before and passed only one soft stool a day. The results of studies on nitrogen balance and calcium and phosphorus balance appear in tables 2, 3 and 4. On March 28 he was placed on a high fat (120 Gm.) diet; within one day severe abdominal borborygmus appeared, with watery, yellow diarrheal stools. Spontaneous tetany also became apparent very rapidly.

While the patient was on the regular house, the low fat and the high fat diet, respectively, studies of the fat content of the feces were made (table 5). Also, while he was still on the low fat diet the basal metabolic rate was determined before and again three hours after the ingestion of 200 Gm. of beefsteak. The basal metabolic rate while he was fasting was —21 per cent; after the ingestion of meat —10 per cent. On another occasion determination of the basal metabolic rate before and three hours after a regular meal produced identical results. A control test with water produced no change. Hypocalcemia with tetany was

From the Department of Medicine, Medical College of Virginia.

1. Supplied by the Valentine Meat Juice Company.

severe; however, it was possible to relieve both with calcium and with vitamin D (table 6, Jan. 9, to May 15, 1941).

The patient was discharged from the hospital on May 2, 1941, with instructions to maintain a high protein, low fat diet and to take vitamin D and calcium lactate. He continued to feel well for a few months, when diarrhea, edema of the ankles and soreness of the tongue reappeared. On August 29 began a one week period of nausea and vomiting, chills and increase of diarrhea. Then injections of crude liver extract were administered for four months without appreciable effect on the moderate anemia, the blood chemistry or the symptoms. Both ingestion of fatty foods and frequent infections of the respiratory tract continued to aggravate the diarrhea. Examination on Jan. 30, 1942 revealed no new physical conditions; the blood pressure was 110 systolic and 60 diastolic. On May 13, 1942 the patient first complained of pain in the left sacroiliac region, radiating down the left leg. The pain was reproduced by straight leg raising, but the neurologic examination revealed nothing significant. Roentgen examination of the spine revealed only slight scoliosis. With symptomatic and supportive treatment symptoms were alleviated gradually over a period of three months.

On August 26 he was again admitted to the hospital. The results of physical examination were unchanged. Sigmoidoscopic examination now revealed no abnormalities except spasm of the lower part of the bowel. Extensive laboratory studies were performed during this hospitalization (reported in a later section of this paper). He was placed on a constant diet containing carbohydrate 350 Gm., protein 125 Gm. and fat 50 Gm. After stabilization on this diet he was given amino acids [2] by mouth, 60 Gm. daily, to determine the effect on his serum protein level (table 6, Oct. 22 to Dec. 12, 1942, and fig. 1). With this regimen his proteins attained the highest level they reached in the total four years of study; he felt well, his symptoms were relieved and edema was minimal. The use of amino acids was soon discontinued, however. Six weeks later he returned with edema of the legs, and hypoproteinemia was again marked. Frequent infections of the respiratory tract appeared, with aggravation of the diarrhea and some manifestations of tetany.

On May 23, 1943 he was readmitted to the hospital. For three weeks he had had respiratory symptoms; one day before admission he suffered a shaking chill with subsequent fever and malaise. On admission his temperature was 104.8 F., his pulse rate 80 and his respiratory rate 18. The blood pressure was 105 systolic and 60 diastolic. The physical examination revealed only moderate generalized abdominal tenderness and distention and slight edema of the ankles. The leukocyte count was 6,800, with 67 per cent polymorphonuclear cells, 1 per cent eosinophils, 2 per cent basophils and 30 per cent lymphocytes. Urinalysis gave normal results. Agglutination reactions with Eberthella typhosa, Salmonella paratyphi B, Brucella abortus and Proteus OX 19 were negative. The blood was sterile on culture, and the sputum consistently failed to reveal the tubercle bacillus. The patient had a constant septic temperature curve and rapidly became extremely ill, with progressive loss of weight. A roentgenogram of the chest taken on May 29 suggested miliary tuberculosis; this was also demonstrated on all subsequent films. Gradually a soft, irregular mass appeared in the abdomen and increased in size under observation. Abdominal distention, vomiting and obstipation were severe, and jaundice was next noted. It was felt, with corroboration by roentgen examination, that there was obstruction in the upper part of the intestine. Laparotomy was performed, and a large retroperitoneal mass was found; the overlying tissues displayed pronounced edema, considered to be due to lymphatic obstruction. Two thousand cubic centimeters of bile-stained fluid was removed from the peritoneal cavity. The mass was thought to be a group of caseating tuberculous mesenteric lymph nodes, and direct smear of the aspirated pus demonstrated myriads of acid-fast bacilli. Biopsy of the mass revealed necrotic granulation tissue compatible with tuberculosis. Postoperatively the patient failed rapidly and died on June 17.

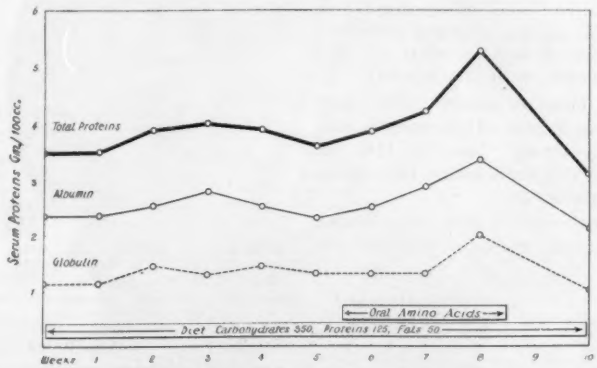

Fig. 1.—Chart illustrating the effect of orally administered amino acids on the serum protein level.

Laboratory Studies.—The hemoglobin content of the blood gradually fell over a period of four years from 105 per cent (100 per cent, 17 Gm. per hundred cubic centimeters) to 80 per cent, with no alteration by any form of treatment. The erythrocyte count ranged

2. Supplied through Dr. F. M. Johnson, Frederick Stearns and Company. The substance administered was a 20 per cent solution of amino acids derived from acid hydrolysis of casein and fortified with tryptophan.

consistently between 4,500,000 and 5,200,000. The leukocyte count varied from 7,000 to 9,000, with the percentage of polymorphonuclear cells from 65 to 75 and eosinophils present consistently. The proportion of reticulocytes varied from 0 to 4 per cent, with no stimulation by any form of treatment. The mean corpuscular volume was 86 cubic microns on Feb. 22, 1939 and 92 on Nov. 14, 1942; the mean corpuscular hemoglobin was 28 and 24 micrograms respectively and the mean corpuscular hemoglobin concentration 33 and 26 per cent.

Serologic tests for syphilis gave negative results. Urinalyses consistently showed the urine to be normal. In a phenolsulfonphthalein excretion test 33 per cent of the dye was recovered in thirty minutes and 55 per cent in two hours. The Mosenthal concentration test showed concentration of the urine to a specific gravity of 1.023.

To determine the function of the liver several tests were made. The prothrombin time was found to be twenty seconds (control, seventeen seconds). In a sulfobromophthalein excretion test almost 100 per cent of the dye was removed from the blood in thirty minutes, and there was total elimination in ninety minutes. The total cholesterol in the blood amounted to 140 mg. per hundred cubic centimeters, free cholesterol constituting 20 mg. and esterified cholesterol 120 mg. In the oral hippuric acid excretion test 3.04 Gm. appeared in the urine in four hours (normal).

The feces were soft, mushy or watery. They were often yellow, and bile was present. Hymenolepsis nana was present inconstantly through June 11, 1940 but was not found thereafter. Mycobacterium tuberculosis was not obtained from the stools.

Analyses of the gastric contents gave the following values for hydrochloric acid (no lactic acid was detected).

	Hydrochloric Acid		
	Free	Combined	Total
2/22/39:			
Fasting	50	14	64
15 minutes after histamine	30	5	35
30 minutes after histamine	63	10	73
45 minutes after histamine	60	11	71
9/11/42:			
Fasting	0	5	5
30 minutes after histamine	0	10	10
45 minutes after histamine	30	10	40

Roentgen studies were made on several occasions. On Jan. 9, 1939, examination after a barium sulfate enema showed an irritable, spastic colon. On March 7, 1941, a similar examination revealed that the spasm of the colon had been greatly relieved. On March 14, 1941, the bone age, as determined roentgenologically, seemed normal; there were no cystic areas, periosteal elevations or thinning of the cortex. On Sept. 5, 1942, roentgenograms of the teeth showed translucency of the bone surrounding all the teeth, indicating probable softness of these bony structures. On September 15, a series of roentgenograms of the gastrointestinal tract revealed extreme hypermotility of the tract, with no hypomotility in any portion; no lesions were seen. On September 18, the lungs appeared clear and the heart normal. On May 29, 1943, fine miliary mottling in both lungs suggested hematogenous spread of tuberculosis. On June 11, 1943, four hours after a small barium sulfate meal there was retention of about one third of the barium in the stomach. Obstruction in the duodenojejunal junction was suggested.

An enzymatic assay of the duodenal contents on Oct. 18, 1942 resulted in the following report: "Amylase activity good; pronounced lipase activity; tryptic activity seems good; bile salts present." The pancreatic secretions were found to be normal.

Chemical studies of the blood gave the following results: The nonprotein nitrogen content ranged between 25 and 35 mg. per hundred cubic centimeters in fifty-two determinations. The total cholesterol content (serum) ranged between 100 and 160 mg. per hundred cubic centimeters in thirty-nine determinations; there was no change which could be correlated with any form of treatment. Table 1 shows the results of dextrose tolerance tests correlated with the basal metabolic rate. Other data on the blood are presented in table 6.

TABLE 1.—*Correlation of Results of Dextrose Tests with Basal Metabolic Rate*

	Dextrose, Mg. per 100 Cc.								Basal Metabolic Rate, %
Date	Fasting	½ Hr.	1 Hr.	1½ Hr.	2 Hr.	2½ Hr.	3 Hr.	4 Hr.	5 Hr.	
1/13/39	76	116	107	107	94	85	61	..	..	−27
3/13/41	130	128	77	...	71	..	75	77	87	−27
9/19/42	85	160	186	...	111	..	81	96	..	−4

TABLE 2.—*Studies of Fecal Fat*

	Per Cent Fecal Fat of Dry Weight of Feces		
	Total Fat	Neutral Fat	Fatty Acids
General diet	28.4	19.2	9.2
High protein, low fat diet	24.3	20.8	3.5
High fat diet	37.7	33.2	4.5

TABLE 3.—*Studies of Nitrogen Balance*

	Intake, Gm.	Excretion, Gm.		Total Excretion, Gm.	Retention, Gm.
		Urine	Feces		
4 day period	61.36	45.12	12.60	57.72	3.64
Daily	15.34	11.28	3.15	14.43	0.91
Per cent of total food nitrogen in feces = 20.5					

The results of studies of fecal fat (April 1941) are shown in table 2. Determinations of nitrogen balance (March 20 to 24, 1941) are presented in table 3, of phosphorus balance (April 4 to 8, 1941) in table 4 and of calcium balance (April 4 to 8, 1941) in table 5.

Tests of the urine with Sulkowitch's solution[3] from Sept. 24 to Dec. 19, 1942 revealed no cloud or only a

3. Two and five-tenths grams of oxalic acid, 2.5 Gm. of ammonium oxalate and 5 cc. of glacial acetic acid are dissolved in distilled water and made up to a volume of 150 cc. (Barney, J. D., and Sulkowitch, H. W.: Progress in the Management of Urinary Calculi, J. Urol. **37**:746, 1937). Five cubic centimeters of this solution is added to an equal amount of urine which is acid to litmus or has been made so with 50 per cent acetic acid solution. If a fine white cloud appears there is a moderate amount of calcium in the urine; this is normal. If there is no precipitation, there is no calcium in the urine.

faint cloud, which indicated an abnormally low urinary content of calcium at this time.

Autopsy.—The body was emaciated and slightly jaundiced. The abdomen was swollen and tense, and there were many hemorrhagic areas over the upper part of the abdomen. The left pleural cavity contained 500 cc. of clear yellow fluid, and the pericardium contained 100 cc. of similar fluid. The heart was small and flabby but otherwise normal grossly. The right lung weighed 875 Gm. and the left 725 Gm. Both pleurae appeared normal. Both lungs were pale and contained air in the anterior third, but the posterior portions were dark, of slate blue color, heavy and solid; on section there was extreme edema. A few small tubercles were scattered in the lungs; the bronchi and trachea appeared normal. The hilar lymph nodes were moderately enlarged and showed mixed anthracosis and caseous mottling on section.

The abdomen contained 1,200 cc. of dark red fluid. In the middle of the upper part of the abdomen appeared a doughy, hard mass, adherent to which anteriorly were parts of the stomach, spleen and intestines; most of the viscera could be freed from this mass. Retroperitoneally was a doughy, semifluctuant mass, 15 by 15 cm. and 6 to 8 cm. thick. Finger dissection caused rupture of the mass, from which yellowish green "pus" escaped; a multilocular structure, i. e., multiple abscesses or caseation of the mass (fig. 2), was revealed. No intra-abdominal lymph nodes could be demonstrated as such, and all lymphatic vessels were obscured by the mass. The liver was enlarged and smooth surfaced. On section it showed engorgement and dilatation of the bile ducts. Many tubercles the size of a small pinhead were scattered throughout. The gallbladder was moderately distended, as well as the whole biliary duct system. The spleen, weighing 550 Gm., was enlarged, dark red and abnormally firm; pinpoint tubercles were thickly scattered throughout the substance. The pancreas appeared normal. The kidneys appeared normal

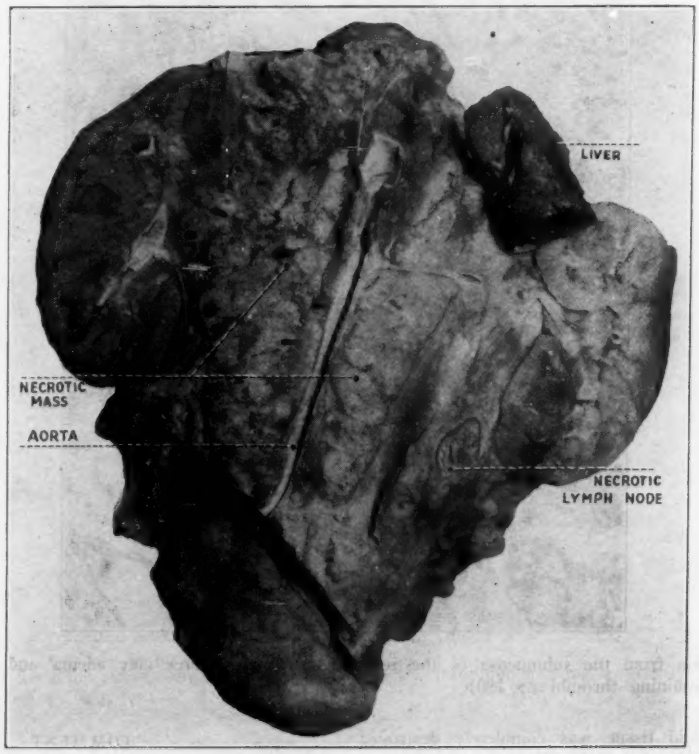

Fig. 2.—Coronal section of the intra-abdominal mass, viewed from the posterior aspect, showing encroachment on other organs.

TABLE 4.—*Studies of Phosphorus Balance*

	4 Day Period	Daily	Total Excretion, %
Urinary excretion (mg.).....	3,443	861	62
Fecal excretion (mg.).....	2,160	540	38
Intake in food (mg.).....	6,504	1,626	
Retention (mg.).....	901	225.2	

TABLE 5.—*Studies of Calcium Balance*

	4 Day Period	Daily	Total Excretion, %
Urinary excretion (mg.).....	72	18	1.6
Fecal excretion (mg.).....	4,360	1,090	96.4
Intake in food (mg.).....	4,301	1,075	
Excretion (mg.).....	131	32.7	

externally; many branching "abscesses" spread from the mesenteric mass into the kidney substance, breaking into the pelvis. The adrenals were small and riddled with miliary tubercles. The stomach and intestines were hyperemic, with small submucous hemorrhages. The intestine was hyperemic in places, with many miliary tubercles in the mucosa, especially toward the terminal portion of the ileum. There were no ulcerations, and the mucosa appeared essentially normal.

Microscopic Examination: The mesenteric lymph node mass was composed of a fibrous tissue framework enclosing multiple small and large areas of blood pigment. The pancreas revealed extreme intralobular edema, and the islets of Langerhans were normal in distribution and number. Section of the duodenum and jejunum showed normal-appearing mucous membrane; there was moderate edema of the submucosa. All the lymphatics of the villi and submucosa were greatly dilated and contained thrombi, composed of some fibrin and many mononuclear cells; the cytoplasm of many of these mononuclear cells (macrophages) appeared foamy (figs. 3 to 5). These changes were interpreted as indications of lymphatic obstruction. There were occasional necrotizing nodules in the submucosa and muscularis.

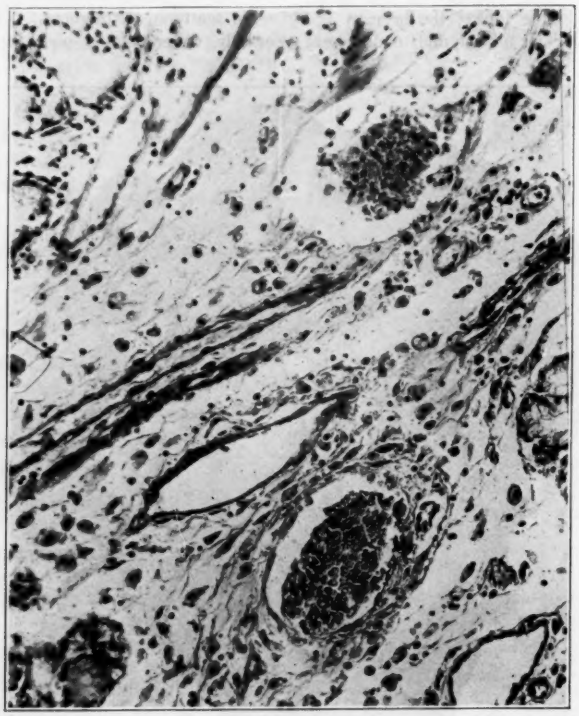

Fig. 3.—Section from the submucosa of the jejunum, showing intercellular edema and marked dilatation of lymphatics containing thrombi (× 180).

necrosis. Lymphoid tissue was completely destroyed by the process, and tubercle bacilli were demonstrated in profusion. The lung showed many miliary nodules, some of which were typical tubercles; others contained fibroblasts, with some necrosis but without giant cells or epithelioid cells. There were pulmonary edema and chronic passive congestion. The heart appeared normal except for mild interstitial edema. The kidney showed miliary nodules composed of a network of fibrous tissue with much necrosis and little cellular reaction; there was nothing to suggest true tubercle formation; the tubular epithelium showed cloudy swelling. No abnormalities of the glomeruli were noted (i. e. crescent formation or endothelial proliferation). The liver, spleen and adrenals all demonstrated similar necrotizing miliary nodules. The liver showed dilatation of the bile ducts with inspissation of bile and atrophy of the central cells of the lobules, probably due to passive congestion. In the spleen there were many deposits of

COMMENT

In 1855 Gull [4] reported the first recorded case of fatty stools from disease of the mesenteric glands. His patient was a 13 year old boy suffering from loss of weight and weakness, but with a huge appetite; the abdomen was distended and enlarged, and intra-abdominal glands were palpable. The patient had steatorrhea with liquid, chalk-colored stools, "frothing like soap when a stream of water was poured on them"; when they were shaken with ether a large amount of fat separated, and ingested cod liver oil was recovered from the stools. Postmortem examina-

4. Gull, W.: Fatty Stools from Diseases of the Mesenteric Glands, Guy's Hosp. Rep. **1**:369, 1855.

tion revealed pulmonary tuberculosis and enlarged tuberculous mesenteric glands. A few other observers have noted the occurrence of defective absorption in mesenteric tuberculosis; attention has been directed mostly to the similarity between this syndrome and the sprue syndrome. Thaysen quoted Rollston's [5] description of patients with chronic fibrous obliterating tuberculosis of the peritoneum and mesenteric lymph glands; the appearance of these patients simulates that of patients with sprue. In 1924 Ryle [6] reported 3 cases, which he presented in support of his hypothesis that the sprue syndrome may be caused by obstruction of the lacteals. The first patient was a 36 year old woman with chronic fatty diarrhea and recurrent tetany since childhood. At operation there was caseating tuberculosis of the mesenteric nodes, with great dilatation of the lymphatics. The other 2 patients were young adults with similar symptoms and intra-abdominal changes. On the basis of these cases Ryle stated that "the causal pathology of celiac disease cannot be regarded as fully investigated until it has been demonstrated at operation or postmortem that there is, or is not, some obstructive lesion in the lacteal system." Ryle's case 1 was followed for eighteen years after the first observation until the patient's death, and a final complete report was made.[7] Symptoms of diarrhea and tetany had continued. At autopsy there was seen chronic tuberculosis of the mesenteric lymph nodes, showing fibrosis and many giant cells with foamy cytoplasm; the fine lacteals in the intestine were slightly dilated.

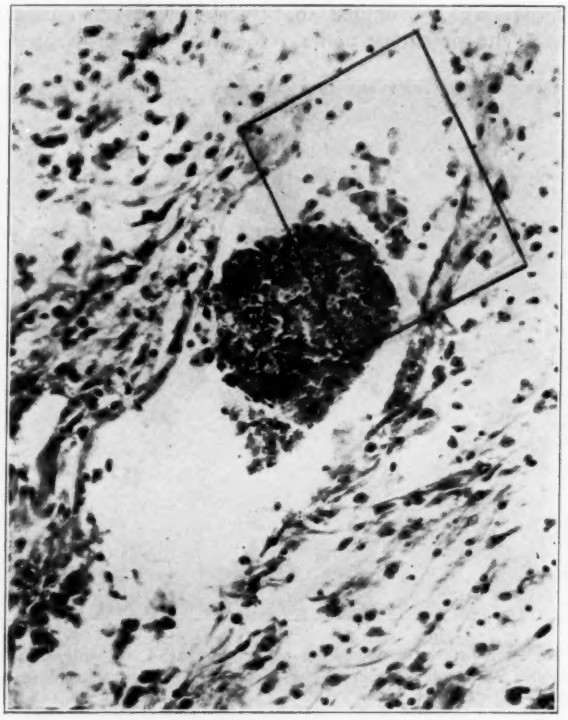

Fig. 4.—Section from the submucosa of the upper part of the jejunum, showing a greatly dilated lymphatic containing a thrombus (× 40).

Mendes Ferreira and Bargen [8] reported the case of a 29 year old woman with a classic sprue syndrome, as proved by chemical and roentgen studies. Biopsy of an axillary lymph node revealed caseating tuberculosis, and at autopsy there was seen also tuberculosis of the hilar and periaortic glands. The mucous membranes of

5. Rollston, F., cited by Thaysen.[22]

6. Ryle, J. A.: Fatty Stools from Obstruction of the Lacteals, Guy's Hosp. Rep. **74**:1, 1924.

7. Hurst, A.; Wright, G. P., and Ryle, J. A.: Sprue Syndrome from Obstruction of the Lacteals by Chronic Tuberculosis of the Mesenteric Lymph Nodes, Guy's Hosp. Rep. **91**:25, 1942.

8. Mendes Ferreira, A. E., and Bargen, J. A.: So-Called Non-Tropical Sprue Associated with Tuberculosis of the Lymph Nodes, Proc. Staff Meet., Mayo Clin. **12**:289, 1937.

the stomach and intestines showed atrophy, and the mesenteric nodes were enlarged, with increase of fibrous tissue, but with no evidence of tuberculosis. This case was later reported in greater detail by Mendes Ferreira,[9] who raised the question of the possibility of blockage of intestinal absorption by tuberculous mesenteric nodes; the authors considered it a mere complication of the sprue syndrome. Warner[10] has also reported a case of tuberculous peritonitis simulating celiac disease in a child, with autopsy observations.

The reported cases illustrating the syndrome of intestinal malabsorption are not limited to instances of tuberculosis of the mesenteric nodes. these cases with symptoms similar to those of sprue there is engorgement of the enlarged mesenteric nodes with fat and fat-containing macrophages. One theory offered as an explanation of the manifestations of this syndrome is that the lymphatic vessels are obstructed by chronic inflammatory changes in the mesenteric lymph nodes. Glynn and Rosenheim[16] studied a 44 year old man with abdominal pain and recurrent fatty diarrhea. There was marked steatorrhea, with relative increase of soaps and fatty acids. Roentgen examination of the gastrointestinal tract showed rapid passage of barium through the small and large intestines. The patient died

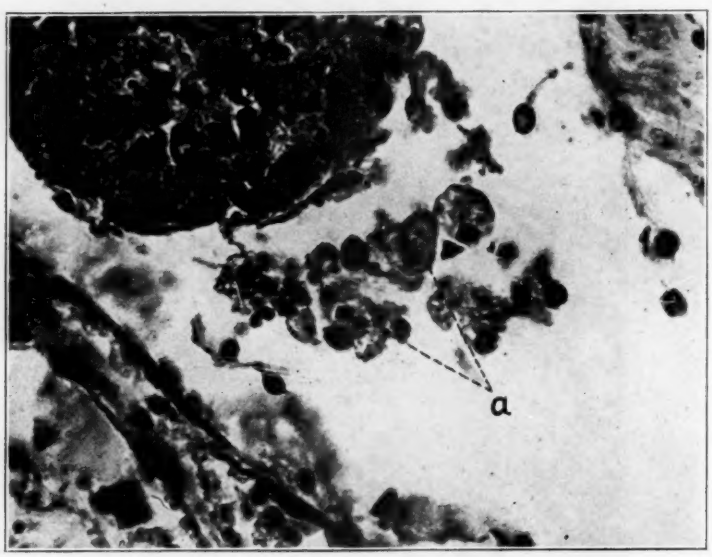

Fig. 5.—Higher magnification of the blocked area seen in figure 4, showing details of the thrombus and the surrounding cells; *a* indicates monocytes (macrophages) containing foamy cytoplasm (× 720).

Whipple[11] was the first to describe a syndrome which he called intestinal lipodystrophy; subsequently cases of a similar syndrome were reported by Reinhart and Wilson,[12] Blumgart,[13] Jarcho,[14] Apperly and Copley[15] and others. In after a year, and at autopsy the mesenteric nodes were enlarged, with large, dilated efferent lymphatics. Microscopically the nodes were cystic, and the cysts were filled with neutral fat and lined with fat-containing giant cells. It has been demonstrated clearly in 4 cases reported by Fairley and Mackie[17] that a clinical and biochemical syndrome of intestinal malabsorption may be associated with various diseases of the mesenteric lymph nodes. Their first patient was an old man with diarrhea, emaciation and tetany. Severe hypocalcemia and steatorrhea with in-

9. Mendes Ferreira, A. E.: So-Called Nontropical Sprue, with Reference to Case Complicated by Tuberculosis of Lymph Nodes, Lisboa méd. **15**:91, 1938.

10. Warner, E. C.: Tuberculous Peritonitis Simulating Celiac Disease, Brit. M. J. **1**:977, 1931.

11. Whipple, G. H.: A Hitherto Undescribed Disease, Bull. Johns Hopkins Hosp. **18**:382, 1907.

12. Reinhart, H. L., and Wilson, S. J.: Malabsorption of Fat, Am. J. Path. **15**:483, 1939.

13. Blumgart, H. L.: Three Fatal Cases of Malabsorption of Fat, Arch. Int. Med. **32**:113 (July) 1923.

14. Jarcho, S.: Steatorrhea with Unusual Intestinal Lesions, Bull. Johns Hopkins Hosp. **58**:275, 1936.

15. Apperly, F. L., and Copley, E. L.: Whipple's Disease (Lipophagia Granulomatosis), Gastroenterology **1**:461, 1943.

16. Glynn, L. E., and Rosenheim, M. L.: Mesenteric Chyladenectasis with Steatorrhea and Features of Addison's Disease, J. Path. & Bact. **47**:285, 1938.

17. Fairley, N. H., and Mackie, F. P.: The Clinical and Biochemical Syndrome in Lymphadenoma and Allied Diseases Involving the Mesenteric Lymph Nodes, Brit. M. J. **1**:375, 1937.

crease of fatty acid content of the feces were present. At autopsy there was pronounced mesenteric lymphoid hyperplasia. Of the other 3 patients, all presented similar symptoms; all suffered with steatorrhea, and 2 had flat oral dextrose tolerance curves. All 3 showed disease of the mesenteric lymph nodes; 1 had Hodgkin's disease, 1 lymphosarcoma and the other an undiagnosed lymphoma. The authors considered the changes in these 4 patients to be due to defective absorption as a result of obstruction of the lymphatic system. Jones [18] questioned whether lymphatic obstruction is not a factor in sprue on the basis of his demonstration of dilated, engorged lacteals and enlarged mesenteric glands during incidental operations on patients with sprue. In 1937 Hill [19] made a complete pathologic study of a patient with "mesenteric chyladenectasis." The clinical history given is inadequate; however, at postmortem examination there was the same lymphatic dilatation, with fat-engorged macrophages and with cyst formation in the lymph nodes. Hill interpreted the changes as indications of lymphatic obstruction. One other notable manifestation of abdominal adenopathy is chylous ascites, also evidence of lymphatic

TABLE 6.—*Blood Chemistry, Basal Metabolic Rate and Therapy*

Date	Calcium, Mg./100 Cc. Total	Calcium, Mg./100 Cc. Diffusible	Total Protein, Gm./100 Cc.	Albumin, Gm./100 Cc.	Globulin, Gm./100 Cc.	Phosphates, Mg./100 Cc.	Basal Metabolic Rate	Therapy and Comments
1939								
1/ 4	6.8	4.82	3.5	2.2	1.3	3.1	....	Oral liver extract, high protein diet and dilute hydrochloric acid
1/19	7.4	5.42	3.5	2.2	1.3	3.5	....	↓
1/30	8.8	6.1	...	...	...	3.5	....	
2/ 9	8.8	6.5	4.1	2.8	1.3	4.3	—27	Add thyroid extract
2/27	9.2	6.3	...	...	...	4.3	—21	↓
3/23	8.6	6.4	3.9	2.5	1.4	3.6	....	
5/ 1	8.0	5.8	3.9	2.0	1.9	3.7	....	
5/20	8.4	6.4	3.6	2.0	1.6	3.1	—32	↓
6/ 5	8.6	6.6	3.5	1.9	1.6	3.7	....	Kaolin and bismuth for diarrhea
6/15	8.8	6.88	3.4	1.9	1.5	4.1	....	
7/ 6	8.6	7.0	2.8	1.6	1.2	4.2	—31	
7/19	9.0	7.1	3.4	1.8	1.6	4.0	....	
8/ 3	9.0	6.8	4.0	2.2	1.8	4.6	—33	
9/ 1	8.6	6.8	3.2	2.1	1.1	3.6	—34	
10/14	8.4	6.5	3.4	1.9	1.5	3.3	....	
1940								
2/23	7.2	5.2	3.5	2.5	1.0	3.1	....	
4/ 2	6.6	4.68	3.4	2.3	1.1	3.3	—33	
6/11	6.6	4.79	3.2	1.5	1.7	4.8	—24	
8/28	7.4	5.6	3.2	1.9	1.3	3.8	....	Symptoms of tetany
10/ 7	6.2	4.73	2.6	1.6	1.0	4.6	—30	↑
1941								
1/ 9	6.4	4.48	3.4	1.9	1.5	3.2	—16	Discontinued oral liver extract, hydrochloric acid and thyroid
3/ 3	6.4	4.37	3.6	2.5	1.1	3.5	—27	High protein, low fat diet; calcium lactate, 6 Gm. daily
3/11	6.2	4.11	3.7	2.5	1.2	2.5	....	Vitamin D (activated ergosterol)
3/27	...	...	3.5	2.4	1.1	3.4	....	↓
4/ 1	5.6	3.74	3.3	2.3	1.0	...	....	
4/ 8	6.8	...	3.3	2.2	1.1	...	—21	
4/10	6.8	...	...	...	...	4.0	....	
4/15	7.6	5.79	3.2	2.2	2.0	4.1	....	↓
4/24	8.6	...	...	...	...	...	....	
5/15	8.6	6.23	4.2	2.8	1.4	4.5	—18	Discontinued vitamin D
8/21	...	...	3.2	2.2	1.0	4.6	....	
9/27	6.8	4.93	3.3	1.9	1.4	4.0	—31	Liver extract intramuscularly
12/ 4	6.6	4.68	3.4	2.2	1.2	3.6	—30	↓
1942								
1/31	...	...	3.6	2.4	1.2	3.6	....	Discontinued liver extract
4/ 2	...	...	2.8	1.8	1.0	...	—14	
4/10	...	...	3.5	2.2	1.3	...	....	Vitamin D
5/13	7.6	5.45	3.8	2.3	1.5	4.1	....	↓
6/10	8.4	6.0	4.2	3.0	1.2	4.5	....	Discontinued vitamin D
7/11	7.8	5.76	3.6	2.4	1.2	3.7	....	
8/15	6.7	5.10	3.3	1.9	1.4	...	....	
9/ 5	6.2	4.7	2.6	1.7	0.9	3.5	....	
10/22	...	...	3.2	2.2	1.0	...	....	Amino acids, 60 Gm. daily (p. o.)
10/29	8.0	5.85	3.8	2.4	1.4	4.4	....	↓
11/ 5	...	...	4.0	2.7	1.3	...	....	
11/10	...	...	3.9	2.5	1.4	...	— 4	
11/17	8.0	6.0	3.6	2.3	1.3	4.9	....	
11/28	...	...	3.8	2.4	1.4	...	....	
12/ 5	...	...	4.2	2.8	1.4	...	....	
12/17	...	...	5.3	3.3	2.0	...	....	Discontinued amino acids
1943								
2/12	8.0	6.3	3.1	2.1	1.0	...	— 6	
3/26	8.2	6.45	3.1	2.0	1.1	3.8	....	
5/24	7.0	4.91	3.7	2.0	1.7	3.9	....	

18. Jones, I. D.: Is Lymphatic Obstruction a Factor in Sprue? Lancet **2**:525, 1924.

19. Hill, J. M.: Mesenteric Chyladenectasis, Am. J. Path. **13**:267, 1939.

obstruction. Pratt and Frew [20] reported this complication in an abdominal lymphadenoma, and Poynton and Paterson [21] have noted a similar phenomenon in a child with nontuberculous enlargement of the mesenteric nodes; diarrhea, suggestive of steatorrhea, also occurred in their patient.

From the beginning the superficial similarity of the condition in the reported case to the sprue syndrome was noted; the changes which suggested this disease were the constant hypoproteinemia, the hypocalcemia, the flat oral dextrose tolerance curve and the slight but definite steatorrhea. However, there were many features which made this diagnosis unlikely: the absence of appreciable anemia, the absence of achlorhydria, the persistently decreased basal metabolic rate and roentgen evidence of increased motility of the gastrointestinal tract. In patients with sprue anemia invariably develops, usually macrocytic in type, and parenterally administered liver extract is effective in the relief of this anemia and the general symptoms of the disease. No such effect was noted in this patient. In his monograph on sprue Thaysen [22] stated that achlorhydria is present in 40 to 50 per cent of cases and hypochlorhydria is common. Gastric acidity was normal in the reported case. The same author also noted that the basal metabolic rate is definitely elevated in every case of sprue. In our patient the basal rate was extremely low for three years, approaching the normal range in the last year of his life. Why the basal metabolic rate should be increased in sprue and not in the malabsorption syndrome described here is not clear; apparently one explanation advanced is that the body derives energy mostly from carbohydrate, with a consequent increase in the respiratory quotient. This is not consistent with the poor carbohydrate absorption manifested by the dextrose tolerance curve. There must be fundamental differences, as yet unexplained. Roentgen examination of the gastrointestinal tract demonstrated increased motility of the whole tract, a finding which differs greatly from the smoothing of all the normal mucosal patterns and marked hypomotility of the intestines seen in sprue and some other fatty diarrheas.[23]

The chemical findings point to severe impairment of absorptive powers, with definite improvement during the year before death. There were no indications of decrease of functional capacity of the liver or kidneys, nor any evidence of pancreatic insufficiency. In 1939 the dextrose tolerance curve showed a rise of only 40 mg. after thirty minutes and fell rapidly to a normal level; in 1941 there was no rise in blood sugar, while in 1942 the patient had a normal dextrose tolerance curve. In each instance the test had been preceded by a high carbohydrate intake. This change alone would indicate improvement in previously impaired absorptive powers and may well be correlated with the increase of the basal metabolic rate (table 1), which rose from a stabilized level of between —20 and —30 per cent to normal, coincident with the increase of absorption of dextrose. Increased absorption of dextrose allowed increased metabolism, and this was reflected in the increase of oxygen utilization (basal metabolic rate). However, in the early period of his illness the evidence for poor absorption of carbohydrate was definite. Along these lines, Ross has carried out two separate studies on patients with abdominal glandular tuberculosis.[24] In every instance he was able to demonstrate a flat dextrose tolerance curve after oral administration of sugar but a high curve after intravenous injection. He felt that these findings indicated defective absorption of carbohydrate from the intestines. The high curve with intravenous administration of sugar was attributed to prolonged carbohydrate deprivation and starvation; this curve was returned to normal by parenteral administration of liver extract.

The constancy of the severe hypoproteinemia even with ingestion of large amounts of protein and in the presence of apparently normal proteolytic enzymes would be strong evidence of poor absorption from the intestines. Many measures were utilized to determine their effect on the serum protein level: oral administration of liver extract and of vitamins, symptomatic treatment of the diarrhea, dietary measures, parenteral injection of crude liver extract and administration of massive doses of calcium and vitamin D. During the four years of study the total protein concentration did not exceed 4.2 per cent. However, when amino acids were administered orally a level of 5.3 per cent total serum proteins was attained, with an albumin fraction of 3.3 per cent (table 6, Oct. 22 to Dec.

20. Pratt, T. A., and Frew, H. W. O.: Chylous Ascites Complicating Abdominal Lymphadenoma, Brit. M. J. **1**:622, 1931.

21. Poynton, F. J., and Paterson, H.: The Occurrence of Ascites of a Non-Tuberculous Origin in Chronic Recurrent Diarrhea in Childhood, Lancet **1**:15, 1914.

22. Thaysen, T. E. H.: Non-Tropical Sprue, London, Oxford University Press, 1932.

23. Kantor, J.: The X-Ray Diagnosis of Idiopathic Steatorrhea, Am. J. Roentgenol. **41**:75, 1939.

24. Ross, C. W.: (*a*) Impaired Glucose Tolerance in Certain Alimentary Disorders of Childhood, Lancet **2**: 556, 1936; (*b*) The Carbohydrate Metabolism in Abdominal Tuberculosis, Arch. Dis. Childhood **11**:215, 1936.

11, 1942 and chart 1). This improvement was striking, and it is supposed that already hydrolyzed protein was more easily absorbed than the products of ingested whole protein, which must have been adequately split. The reason for this difference cannot be stated at present; since the amino acids were administered in 1942, it is possible that the response indicates general improvement in absorptive capacity. The studies in 1941 revealed some definite impairment in absorption of amino acids. The average daily excretion of nitrogen in the urine was 11.2 Gm. and in the feces 3.1 Gm. (table 3). The normal daily urinary excretion of nitrogen is 13 Gm. or greater, with no more than 1.3 Gm. per hundred cubic centimeters in the feces.[25] Although our patient did manifest a slightly positive nitrogen balance, the increase of fecal nitrogen, with a percentage of total food nitrogen in the feces of 20.5 per cent (normal, 10 to 12 per cent), is an indication of impaired absorption. In the average normal person, ingestion of pure protein will cause an increase in heat production of 30 per cent, due to the specific dynamic action of the protein.[26] Ingestion of carbohydrate and of fat will produce lesser changes, + 5 per cent and + 13 per cent respectively. This increase in heat production is reflected in the measurement of oxygen utilization. If the increase in heat production and in oxygen utilization is less than the expected rise after ingestion of pure protein, one may infer that absorption of the protein is defective. After the patient had eaten 200 Gm. of beefsteak his oxygen utilization rose from 195 cc. per minute (basal metabolic rate, — 21 per cent) to 224 cc. per minute (basal metabolic rate, — 10 per cent). This represented an increase of 12.9 per cent, or slightly more than a third of the expected rise due to the specific dynamic action of the protein. After ingestion of a meal, the increase was from 200 cc. (basal metabolic date, — 21 per cent) to 228 cc. (basal metabolic rate, — 10 per cent), or a rise in oxygen utilization of 12.4 per cent, again far less than expected. So the hypoproteinemia was apparently due to defective absorption from the intestinal tract.

Studies of the phosphorus balance showed it to be positive and essentially normal (table 4). From 45 to 60 per cent of the phosphorus excreted by the average healthy person appears in the urine, and this was true for our patient. The level of phosphorus in the serum was high normal throughout the whole period of study (table 6). On the other hand, there were definite evidences of impairment of absorption of calcium. Hypocalcemia was constant; this was present even when calcium was given therapeutically in appreciable amounts. The only factor which seemed to aid in elevating the serum calcium level was the administration of vitamin D in large doses (table 6, March 11 to May 15, 1941 and Dec. 6, 1941 to June 10, 1942). Such a response is known to occur in sprue with hypocalcemia, and administration of vitamin D is part of the accepted treatment for that disease. In consideration of this Bassett and associates,[27] carrying out careful balance studies on patients with idiopathic steatorrhea, found that oral administration of large doses of vitamin D caused increased absorption of calcium and phosphorus from the intestine and some increase of absorption of fatty acids also. To a certain extent the level of calcium in the serum was also a function of the severity of the diarrhea; however, even in the presence of severe diarrhea the level was improved with large doses of vitamin D (activated ergosterol). Studies on calcium balance supported the impression of defective absorption (table 5). A normal adult on an ordinary diet has a positive calcium balance; the daily excretion in the feces averages 400 to 700 mg. (65 to 75 per cent of the total calcium excreted), and that in the urine averages 150 to 180 mg. (25 to 35 per cent).[25] Our patient's daily fecal excretion of calcium was 1.090 Gm. and his urinary excretion 18 mg.; this indicates obvious deficiency of absorption, even when with a high calcium intake. Later tests of the urine with Sulkowitch's solution corroborated this finding. As might be expected, there was a very slight negative calcium balance.

The fecal content of total fat is considered normal if it exceeds 28 per cent of the dry weight of the feces. If the neutral fat content is greater than 11 per cent of the total dry material or 55 per cent of the total fat, deficiency of fat-splitting enzymes is suggested.[28] The data on our patient (table 2) are inconsistent with the later finding of "marked lipase activity" and cannot be explained. With a normal diet and a low fat diet, the values for total

25. Best, C. H., and Taylor, N. B.: The Physiological Bases of Medical Practice, ed. 3, Baltimore, Williams & Wilkins Company, 1943.

26. Harrow, B.: Textbook of Biochemistry, ed. 2, Philadelphia, W. B. Saunders Company, 1941.

27. Bassett, S. H.; Keutmann, E. H.; Hyde, H. V., and Van Alstine, H. E.: Metabolism in Idiopathic Steatorrhea: II. Effect of Liver Extract and Vitamin D on Calcium, Phosphorus, Nitrogen and Lipid Balances, J. Clin. Investigation **18**:121, 1939.

28. Fowweather, F. S.: The Determination of the Amount and the Composition of Fat of Feces, Brit. J. Exper. Path. **7**:7, 1926.

fecal fat were at the upper limits of normal, while there was a considerable elevation when ingestion of fat was increased. This is probably a greater increase than might be expected for a normal person. In 1933 Morton,[29] studying 18 patients with tuberculosis of the mesenteric glands, found that the fecal fat content averaged 29.4 per cent of the total dry weight; with his method the normal range was 16 to 21 per cent. As a further control, determinations of the total fecal fat of patients with pulmonary tuberculosis and secondary intestinal lesions produced average results of 16.9 per cent. Morton expressed the belief that in cases of tuberculosis of the mesenteric lymph nodes the fecal fat content is an excellent index of the clinical course and of the prognosis of the disease. Even without studying the condition pathologically, he interpreted the changes that occurred as follows:

> . . . whenever there is tuberculous disease of one of these (mesenteric) glands, part or whole of the gland must be put out of action, and depending on the extent of the damage, smaller or larger numbers of the intraglandular vessels would cease to function. The chyle, finding its means of egress from the gland closed, would first cause dilatation of the afferent vessels, and finally there would be complete stagnation of chyle between the particular lymphatic gland and the area of intestinal mucosa with which it corresponds. For a time at least, the hypertrophy of adjacent glands would compensate for this deficiency in fat absorption, but later this might become so seriously disorganized that much less fat would be absorbed and the percentage amount of fat in the feces would be raised.

This must have been the chain of events which took place in our patient; his stools were frequently yellow and mushy, and the fecal fat content was undoubtedly higher at times even than the slightly elevated values obtained. There was pathologic evidence in the finding of macrophages with foamy cytoplasm (figs. 2 to 4): these changes appear similiar to those demonstrated by Ryle [6] in his case in which autopsy was performed.

The possibility of the edema and hypoproteinemia being due to renal disease was dismissed by consistent normal results of urinalyses and of tests of renal function. Moreover, there were never any evidences of hepatic insufficiency by the tests used. Although the feces contained the ova of Hymenolepis nana irregularly for the first two years of study, it was felt that this parasite played no role in the patient's illness. Undoubtedly his terminal illness indicated extension of the tubercle bacilli up the thoracic duct into the blood stream, with subsequent miliary infection. The original tuberculous infection must have originated from the ingestion of contaminated milk during childhood. Miliary spread is not an unusual cause of death of patients with tuberculous mesenteric adenitis. However, the syndrome of malabsorption from the intestines is not at all common, even though Thaysen listed it among the diseases to be differentiated from sprue. As stated previously, this syndrome is not peculiar to tuberculosis of the mesenteric nodes, since it has been observed in other diseases of these glands; nevertheless, in his review Foster [30] did not mention it among eighteen possible complications of mesenteric adenitis. It is uncommon, yet important enough to be considered frequently. The constant evidence of decreased absorption of most of the food elements without the development of appreciable anemia is noteworthy. Certainly the factors necessary for formation of blood must have been absorbed adequately. This inconsistency leads one to suspect that there may possibly have been a basic disorder of protein metabolism to account for the chemical and biochemical picture; such an explanation appears less logical than the interpretation offered previously. It must be noted that some of the anatomic changes appeared rather acute, and it is likely that there was a rapid spread of the intra-abdominal disease in the several weeks preceding the patient's death. In addition to all the manifestations of chronic malabsorption, there were also pathologic evidences of more recent lymphatic obstruction.

Drs. J. C. Forbes and F. L. Apperly gave advice and helpful criticism.

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29. Morton, W. H.: Abdominal Glandular Tuberculosis: A Study with Special Reference to Fecal Fat Content, Edinburgh M. J. **40**:117, 1933.

30. Foster, A. K.: Diseases of the Lymph Nodes, Arch. Surg. **36**:28 (Jan.) 1938.

Progress in Internal Medicine

BLOOD

A REVIEW OF THE RECENT LITERATURE

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(Continued from page 77)

GRANULOCYTOPENIA AND AGRANULOCYTOSIS

Agranulocytosis following the use of sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine continues to receive notice in the literature of 1943. The communication of Nixon, Eckert and Holmes is of interest, for these observers found that in 3 patients in whom agranulocytosis developed after the use of sulfadiazine recovery ensued despite the fact that they continued to receive large amounts of the drug. Such an observation may cause a revision of ideas concerning sensitivity to various substances. Of great importance is the report of a fatal case of agranulocytosis which was associated with the administration of succinylsulfathiazole. Two more cases of agranulocytosis following the use of quinine in malaria therapy are reported. No new information concerning the relative merits of the various forms of treatment which have been employed in the past few years is available. Of undoubted importance is the observation by Axelrod and his associates that the leukopenia and granulocytopenia which develop in rats as a result of ingestion of a purified diet containing sulfaguanidine can be prevented or cured by the administration of liver or a norite eluate of this organ. Furthermore, it was found by Daft and Sebrell and others that crystalline "folic" acid is active in correcting the leukopenia and granulocytopenia induced in rats by feeding sulfaguanidine or sulfasuxidine. Such observations point to possible new leads in determination of the cause of agranulocytosis and in its treatment.

Etiology.—In a review of the etiology of malignant neutropenia, Gordon [220] states that at present the cause of the disease is debatable. In his opinion, the most plausible theory relating to the mechanism of the disease is, first, a primary involvement of the bone marrow, resulting in a decreased formation of granulocytes, which causes a lowering of the patient's resistance. This terminates in intercurrent infection, necrosis of the mucous membranes and the skin and, finally, death. He lists the following possible causes of the disease: (1) neutropenia following chronic Vincent's angina; (2) severe sepsis affecting myeloblastic tissue and bone marrow; (3) chronic illness; (4) toxic substances depressing or paralyzing bone marrow activity; (5) secondary invasion by bacteria in tissues with lowered resistance; (6) chemical poisoning, as with benzene; (7) drug poisoning with barbital, aminopyrine or a sulfonamide drug; (8) allergy; (9) endocrine disturbances, and (10) possible congenital absence of a necessary substance in bone marrow which makes the person susceptible to the development of leukopenia. Gordon minimizes the importance of the action of various drugs in the causation of the disease, which is in sharp contrast to the experience of the reviewers and many others who have studied this problem. He states that only a small percentage of patients with malignant neutropenia have previously ingested drugs which might have caused the condition and reports that only 1 patient in his group of 97 might have taken a causative drug. In his opinion, the evidence in favor of an allergic or endocrine cause is still scant and unconvincing. He believes that in a large percentage of the cases there is a congenital deficiency of the bone marrow. According to him, this view is supported by those instances in which malignant neutropenia developed in 1 member of a family while myelogenous leukemia occurred in another, and also by the occurrence of neutropenia in 2 persons in one family. In the opinion of the reviewers, these arguments fail to prove his point, as they are indirect and are far from decisive.

Of great importance is the report by Nixon, Eckert, and Holmes [221] of 3 patients in whom agranulocytosis developed after the administration of sulfadiazine but who recovered despite the fact that they continued to receive the drug in large amounts. Those 3 patients were all young men, of whom 2 had atypical pneumonia and 1

220. Gordon, W. H.: Etiology of Malignant Neutropenia, J. Oklahoma M. A. **36**:376, 1943.

221. Nixon, N.; Eckert, J. F., and Holmes, K. B.: The Treatment of Agranulocytosis with Sulfadiazine, Am. J. M. Sc. **206**:713, 1943.

scarlet fever. There can be no question of their having agranulocytosis, as the clinical picture was typical and the white blood cell counts fell as low as 200, 130 and 600 per cubic millimeter respectively, with absence of neutrophils. They had received sulfadiazine in a total dose varying from 52 to 72 Gm. over a fairly protracted period early in the course of their illness. In the first patient, who was suffering from scarlet fever, the total white blood cell count fell to 200 per cubic millimeter, and it was thought that he would certainly die of the overwhelming infection which was present. On the basis that the scarlet fever might be the cause of the agranulocytosis, it was decided to administer sulfadiazine. Hence a sufficient quantity of the sodium salt of the drug was given intravenously to raise the blood level of the drug to 20 to 25 mg. per hundred cubic centimeters. This was followed by a dramatic recovery of the patient. The other 2 patients, in whom a striking decrease in the white blood cell count followed the use of sulfadiazine, were suffering from "virus pneumonia." It was thought that the sulfadiazine must be responsible for the remarkable decrease in the total white blood cell count in these 2 patients. As sulfadiazine therapy had been so successful for the preceding patients, it was given to each of these men, with gratifying results. These observations are of the greatest importance in the study of the causation of agranulocytosis with respect to the role which might be played by sulfonamide compounds, especially sulfadiazine. A sufficient number of cases have been reported of agranulocytosis following the use of this drug which indicate that it is probably of importance from an etiologic standpoint. On the other hand, no one has administered this preparation to a patient thought to be sensitive to it and produced a reduction in the white blood cell count, as has been done with aminopyrine. This would be the most certain proof of an etiologic relationship. In this connection, it is of interest to note that in case I, reported by these authors, acute follicular tonsillitis developed six weeks after the patient's discharge from the hospital following recovery from agranulocytosis, and at this time, on the second admission, he was given 35 Gm. of the drug over a period of five days without a demonstrable effect on the blood picture. The authors conclude that, despite the primary role played by sulfadiazine in causing agranulocytosis, the bone marrow may recover from the temporary depression, even with continued or subsequent administration of large amounts of the same drug. They believe that the patient in whom agranulocytosis develops, regardless of the cause should be given one of the sulfonamide compounds, preferably sulfadiazine, in amounts sufficient to maintain a blood level of approximately 10 to 20 mg. per hundred cubic centimeters until such time as the temporary depression of activity of the bone marrow is overcome and the normal protective mechanism is again functioning. They recommend sulfadiazine because in their opinion it is least likely to cause serious toxic reactions. We admit that the sequence of events in these cases introduces a new thought concerning the possible role played by the sulfonamide compounds in the production of agranulocytosis. It seems clear that these drugs, including sulfadiazine, may cause the disease in certain persons who are sensitive to them. To give a drug which is thought to be responsible for the condition seems illogical and hazardous, but certainly in the reported cases there seems to be no escape from the conclusion that at least the preparation did not interfere with the recovery of the patients when death seemed imminent. Regardless of this report, we should with reluctance continue the use of sulfadiazine for a patient with agranulocytosis in whose case it is thought that the drug was the original cause of the disease. On the other hand, it is conceded that the death of such patients must be attributed to sepsis. A more ideal preparation for the management of the severe infections of such patients may prove to be penicillin, for no reports so far have linked this effective therapeutic agent with the disease.

Mottram [222] emphasizes the importance of information contained in a communication by Britton in the *Lancet,* in which attention is directed to the low leukocyte counts occurring among healthy nurses of the Middlesex Hospital who had not been exposed to radium. Mottram considers that this is a wartime effect which merits investigation to see how far it extends in the population and to seek its cause.

Two cases of granulocytopenia following administration of sulfonamide compounds are reported by Catarinich and Hurley.[223] In a patient with cerebrospinal meningitis a white blood cell count of 1,700 per cubic millimeter with 24 per cent of neutrophils was noted on the twenty-first day after treatment had been instituted with sulfapyridine. During this interval 99 Gm. had been given, but the condition was not discovered until four days after the last dose had been administered. Recovery followed the use of pentnucleotide. The second patient, who had pneumonia, received a total dose of 18 Gm. of sulfapyridine and 24 Gm. of sulfathiazole in

222. Mottram, J. C.: Leucocyte Counts in Radium Workers, Lancet **2**:588, 1943.

223. Catarinich, F., and Hurley, J. J.: Granulocytopenia Complicating Administration of Sulphonamides; Report of Two Cases, M. J. Australia **1**:511, 1943.

eighteen days. On the seventeenth day of treatment, the white blood cell count was 1,600 per cubic millimeter and "only a very occasional" granulocyte was observed. Recovery of this patient also followed treatment with pentnucleotide. It is emphasized by the authors that it is probably unwise to resume the administration of a sulfonamide compound after an interval of seven days without a preliminary leukocyte count, as reactions presumably due to previous sensitization have been reported following such readministration. They conclude that estimations of the level of the sulfonamide compound in the blood, together with leukocyte counts and examination of blood films made at the end of a course of therapy and once or twice during the subsequent week or so will provide a warning signal. We should like to emphasize that in *both of these patients a rash developed on the eighth day* but despite this further treatment with the sulfonamide compound was given. According to our experience, the appearance of cutaneous changes is always an ominous sign which indicates that if the treatment is continued it should be controlled with daily white blood cell and differential counts. With the slightest evidence that these cells are diminishing in numbers, administration of sulfonamide compounds should be completely discontinued, as further treatment is likely to produce fully developed agranulocytosis.

A case of agranulocytosis following sulfapyridine therapy is reported by Baker and Fenner.[224] The patient had been given about 25 Gm. of sulfapyridine for bronchopneumonia when the treatment was discontinued on account of the appearance of a morbilliform rash. A few days later administration of the drug was resumed in a dosage of 5 Gm. twice daily. After the patient had received this dose for about three days, the treatment was again discontinued, because of toxic symptoms. Two days later it was found that the white blood cell count was 2,500 per cubic millimeter with 53 per cent polymorphonuclear cells. On the twenty-third day of the illness, the neutrophils numbered 150 per cubic millimeter, which is the lowest count observed. A total dose of sulfapyridine of about 50 Gm. was given. Recovery followed the administration of 100 cc. of pentnucleotide and blood transfusions.

Carley and Reid[225] discuss the complications of therapy with sulfonamide compounds and record 3 cases of agranulocytosis, in 2 of which it was caused by sulfathiazole and in 1 by sulfanilamide. One patient, a woman aged 43 with pneumonia, received approximately 116 Gm. of sulfathiazole over a period of about four weeks, at the end of which time she was found to have a white blood cell count of 940 per cubic millimeter with 5.5 per cent granulocytes. Death occurred despite withdrawal of the drug, four transfusions of citrated blood and administration of pentnucleotide and nicotinic acid. A second patient, a woman aged 36 with a sore throat and an infection of the middle ear, had a white blood cell count of 1,250 per cubic millimeter with 9 per cent granulocytes after receiving 4.5 Gm. of sulfanilamide in forty-four hours. The course was mild, as she recovered without therapy within five days. The third patient, a girl aged 12 years, was given sulfathiazole for fever without obvious cause in a total dose of 6 Gm. over a period of forty-eight hours. At the end of this time she showed collapse, dyspnea and a sore throat, with a white blood cell count of 300 per cubic millimeter. Recovery occurred spontaneously. The authors of this article conclude that the value of blood transfusions is debatable, as is the use of pentnucleotide and of marrow substances. They state that until more is known concerning the mechanism underlying the granulocytopenia, it is doubtful that there will be any wholly satisfactory treatment. These impressions, however, we wish to emphasize, are apparently based on a review of the literature rather than on the treatment of a convincing number of patients.

A case of acute agranulocytosis following sulfathiazole therapy with recovery in a 55 year old Negro with a compound fracture is reported by Allen and Jackson.[226] A total of 27 Gm. of the drug was given orally, and an additional 2 Gm. of sulfanilamide was applied directly to the wound by insufflation. After the development of an erythematous rash on the chest and abdomen, the white blood cell count was found to be low. It continued to fall until on the tenth day after use of the drug had been discontinued it was found to be 975 per cubic millimeter with only 8 per cent polymorphonuclear cells. Recovery followed the use of large doses of liver extract given intramuscularly, a diet high in calories and vitamins, vitamin B complex, and dextrose administered parenterally. Among the 29,868 patients admitted to the Veterans Administration Facility, Tuskegee, in the twenty years of its operation, the man whose case is reported is the second patient in whom this complication

224. Baker, B. A., and Fenner, F.: Agranulocytosis Following Sulphapyridine Therapy, M. J. Australia **1**: 347, 1943.

225. Carley, P. S., and Reid, P. E.: Granulocytopenia Resulting from Sulfonamide Therapy: Case Reports and Discussion, Urol. & Cutan. Rev. **46**:19, 1942.

226. Allen, R. L., and Jackson, J. E.: Acute Agranulocytosis, Caused by Sulfathiazole, in Negro; Recovery of Patient, M. Bull. Vet. Admin. **19**:460, 1943.

has been recognized, despite the abundant use of sulfanilamide in this institution.

White [227] reports the case of a 10 year old boy in whom agranulocytosis developed after sulfathiazole therapy. The patient had eczema in infancy and impetigo a few years before the onset of the present illness. His illness began with symptoms of an infection of the upper respiratory tract, which progressed into bronchopneumonia within a few days. Sulfathiazole was given in doses of 0.5 Gm. every four hours. Within twenty-four hours the mucous membranes of the mouth showed large vesicles and the body was covered with numerous pemphigoid bullae. The lowest white blood cell count was 4,500 per cubic millimeter with 40 per cent neutrophils. A total of 54 Gm. of sulfathiazole was given over a period of nine days. It would be difficult to prove that this was a case of agranulocytosis due to a sensitivity to sulfathiazole. The possibility that the patient had pemphigus with leukopenia due to a severe infection must be given serious consideration.

Acute fatal agranulocytosis in association with subacute bacterial endocarditis superimposed on a patent interventricular septal defect is reported by Flink and Bratrud.[228] Death occurred within twenty days after the therapy with sulfadiazine had been instituted. A total of 54 Gm. was administered. At the time the last dose was given, it was found that the white blood cell count was 950 per cubic millimeter and the neutrophil count 42 per cent. Later the white blood cell count fell to 500 per cubic millimeter and neutrophils disappeared entirely from the circulating blood. The case observed by Flink and Bratrud represents the only case in which fatal agranulocytosis had developed in the University of Minnesota Hospitals following the use of any of the sulfonamides. No mention is made concerning any prior administration of sulfonamide drugs to the patient.

Lobar pneumonia complicated by fatal agranulocytosis in a patient who received sulfathiazole therapy was observed by McNamara.[230] Within sixty hours after the onset of the pneumonia, as nearly as can be estimated from the case report, the patient had been given 3.5 Gm. of the drug, and at that time the white blood cell count was 1,100 per cubic millimeter and no granulocytes were seen in the blood film. The patient died within twelve hours after admission to the hospital and seventy-two hours after the onset of the disease. As the author states, the most interesting feature of the case is the rapidly fatal course of the lobar pneumonia, which he attributes to the associated agranulocytosis. It is concluded that leukopenia progressing to agranulocytosis may be a rare complication of many severe infections, including lobar pneumonia. In the case reported, it is thought that the agranulocytosis may have been due to the infection rather than to the sulfathiazole since only 3.5 Gm. of the drug was administered. We agree that agranulocytosis following such a small dose of sulfathiazole would be most unusual. No mention is made, however, of previous medication with sulfathiazole or other sulfonamide drugs which might have sensitized the patient to subsequent doses.

Three cases of fatal agranulocytosis due to sulfadiazine therapy are reported by Hettig and Sturgis.[231] In each case the total amount of the drug ingested was in excess of 70 Gm., although the dose given 1 patient was only 2 Gm. daily. Hence it can be concluded that relatively small daily doses do not eliminate the danger of agranulocytosis. None of the patients had previously received any sulfonamide compound. All 3 had been receiving an inadequate diet, and 1 had outspoken pellagra. The authors suggest the theory that a vitamin deficiency may render persons more susceptible to certain drugs and that this may explain some of the aspects of the causation of the disease. They believe it is a plausible interpretation of the occurrence of agranulocytosis as a "new" syndrome, because there is evidence to indicate that at least mild degrees of vitamin deficiencies are more prevalent now than previously. Furthermore, it may explain why some persons are sensitive to certain drugs and others are not. Some corroborative experimental evidence which lends support to this suggestion is found in the work of Day and his associates.[232] They report a leukopenia with white cell values as low as 700 cells per cubic millimeter in monkeys fed the Goldberger black tongue–producing diet. This possible etiologic relationship is suggested by Hettig and Sturgis in the hope that more patients in whom the syndrome of agranulocytosis develops will be studied from the standpoint of nutritional deficiency. By the collection of reliable clinical data it should be possible to settle definitely the relation, if any, of vitamin deficiencies to the causation of the disease.

227. White, G. E.: Sensitivity to Sulfathiazole: Report of a Fatal Case, Canad. M. A. J. **49**:317, 1943.

228. Flink, E. B., and Bratrud, T. E.: Agranulocytosis Associated with Sulfadiazine Therapy, Minnesota Med. **26**:898, 1943.

229. Footnote deleted by authors.

230. McNamara, F. P.: Lobar Pneumonia with Acute Agranulocytosis, J. Iowa M. Soc. **33**:58, 1943.

231. Hettig, R. A., and Sturgis, C. C.: Sulfadiazine Agranulocytosis, J. Michigan M. Soc. **42**:959, 1943.

232. Day, P. L., and others: Nutritional Cytopenia in Monkeys Receiving Goldberger Diet, J. Exper. Med. **72**:463, 1940.

Of the greatest importance is the recording by Johnson [233] of the first fatal case of agranulocytosis attributed to succinylsulfathiazole. This observer reports the case of a 19 year old youth who was treated with succinylsulfathiazole for what was thought to be a moniliasis of the skin and gastrointestinal tract. He was first given sulfathiazole in doses of 1 Gm. three times daily, but its use was discontinued on account of chilliness, malaise, dizziness and loss of appetite. As he had received an injection of 30,000,000 killed typhoid bacilli on the day previous to the sulfathiazole medication, it was first assumed that the vaccine was responsible for the reaction. After a lapse of approximately four weeks without treatment, he was given 15 Gm. of sulfathiazole over a period of six days. Simultaneously with the first dose of the drug he was given an injection of 35,000,000 killed typhoid bacilli. This was promptly followed by an emesis with chills, muscular pains and fever, which persisted for six days. It was first thought that the typhoid vaccine was responsible for these symptoms, but the duration of the febrile response was so long that the sulfathiazole had to be considered as its cause. After a lapse of six months without treatment, the patient was again admitted to the hospital with the same dermatologic complaints. As it was thought that he was suffering from moniliasis of the gastrointestinal tract as well as of the skin, he was given for the first time succinylsulfathiazole, 3 Gm. every three hours. After he had taken 18 Gm. of the drug, there were flushing and a chill, followed by nausea and vomiting. At this time, the sulfathiazole level in the circulating blood was too low to be read. Eighteen days after he received the first dose of the succinylsulfathiazole, 20,000,000 killed typhoid bacilli were injected. On the following day, dizziness and nausea were present, and on the next day the patient complained of sore throat, fever and difficulty in swallowing. Two days after the injection of typhoid bacilli the white blood cell count was 1,400 per cubic millimeter, with a differential count of polymorphonuclears 30 per cent, small lymphocytes 62 per cent and mononuclears 8 per cent. About forty-eight hours later, which was the day before death, the white blood cell count was 200 per cubic millimeter with a differential count of small lymphocytes 14 per cent and large lymphocytes 86 per cent. A sternal puncture at this time showed that maturation of the white blood cells had stopped at the primitive blast and myeloblast stages. Death occurred after the patient had taken 159 Gm. of succinylsulfathiazole over a period of seventeen days. Johnson states that, since succinylsulfathiazole is partially hydrolyzed to sulfathiazole, the febrile response was no doubt due to sensitization to sulfathiazole. According to him, sensitization has been shown to be present not only when there is interruption in the course of the medication but when there has been prolonged administration of large doses of the drug. In his opinion, both of these conditions were present in this case. Poth [234] comments on the article by Johnson in a letter addressed to the Editor of *The Journal of the American Medical Association*, in which he does not fully agree with the conclusions of Johnson's article. In the same issue is a reply by Johnson which appears to answer his criticism satisfactorily.

It is of interest to note that agranulocytosis developed in a patient with exophthalmic goiter who had been treated with a derivative of thiourea (thiouracil) for the toxic manifestations of the disease. According to Astwood,[235] the patient had received from 1 to 2 Gm. of the drug for a period of thirty-six days, after which time a severe pharyngitis developed and his body temperature was 105 F. The white blood cell count was found to be 1,100 per cubic millimeter, and there were no demonstrable granulocytes in the circulating blood for seven days. They returned after administration of sulfathiazole, liver extract and pentnucleotide. During the patient's stay in the hospital it is probable that he did not receive other drugs which might have been responsible for the striking decrease in the leukocytes. The condition developed within thirty-six hours after his discharge from the hospital, and during that interval he might have ingested other drugs responsible for the condition, but no mention is made of this by the author.

Relation of Malaria and Quinine Therapy to Agranulocytosis.—The development of agranulocytosis following the use of quinine in malaria therapy is reported in the case of a 26 year old soldier by Franks and Davis.[236] The patient was given 5 grains (0.3 Gm.) of quinine sulfate three times daily. Within twenty-four hours a leukopenia was apparent, and this progressed until

233. Johnson, S. A. M.: Acute Agranulocytosis Due to Administration of Succinylsulfathiazole, J. A. M. A. **122**:668 (July 3) 1943; Granulocytopenia After Use of Succinylsulfathiazole, correspondence, ibid. **123**:112 (Sept. 11) 1943.

234. Poth, E. J.: Granulocytopenia After Use of Succinylsulfathiazole, J. A. M. A. **123**:112 (Sept. 11) 1943. (Comment on Johnson.[233])

235. Astwood, E. B.: Treatment of Hyperthyroidism with Thiourea and Thiouracil, J. A. M. A. **122**:78 (May 8) 1943.

236. Franks, A. G., and Davis, M. I. J.: Agranulocytosis: Complication Following Quinine in Case of Malaria Therapy, Am. J. Syph., Gonor. & Ven. Dis. **27**:314, 1943.

five days after the onset, when the leukocyte count fell to 200 per cubic millimeter with 97 per cent lymphocytes. No other drugs were given to the patient except acetylsalicylic acid, phenobarbital and codeine, which had been used in the usual doses at widely separated intervals; none of these drugs had been given for at least ten days prior to the change in the blood picture. Recovery followed the intramuscular use of liver extract and of pentnucleotide solution. The authors state that previously quinine has not been clearly incriminated as a factor in the causation of agranulocytosis, but they consider that in the present case the timing and the sequence of events are such as to leave little doubt as to the responsible agent. We agree that the evidence is suggestive but believe that it is far from conclusive.

Heldt and Goder [237] report a similar instance in which agranulocytosis followed malaria therapy for dementia paralytica. A 45 year old man had a white blood cell count of 750 per cubic millimeter, without granulocytes, after his inoculation with blood from another patient with malaria. The possibility that the agranulocytosis arose from an idiosyncrasy to quinine must be considered, but in the authors' opinion this is not likely. A review of the literature indicated that such a complication of malaria therapy is exceedingly rare. Two cases have been reported by Meyer [238]; 1 patient died and the other recovered. Two similar cases were reported by Jacobson and Abel [239]; both of their patients recovered. In none of the cases was there any clear evidence that quinine was concerned with the agranulocytosis, nor was there any indication that the strain of malaria plasmodium was at fault. According to the authors, the only reference in the English literature to a similar complication of malaria therapy is to be found as a footnote in Moore's textbook on the treatment of syphilis,[240] in which he noted that he had observed 3 patients treated with malaria in whom leukopenia developed, with white blood cell counts varying from 800 to 2,000 cells per cubic millimeter and granulocyte percentages which ranged from 10 to 35. There was no associated angina, and apparently all the patients recovered. He had not observed a similar condition in 600 patients who had been treated with malaria.

Miscellaneous Observations on Agranulocytosis and Leukopenia.—The second fatal case in the literature of agranulocytosis due to novaldin, a drug closely related to aminopyrine, is reported by Moloney and Vidoli.[241] The patient was a 55 year old woman suffering from arthritis of the spine. She was given novaldin in an attempt to control the pain. After she had received approximately 4 Gm., a white blood cell count was made because the patient was thought to have some condition in the abdomen possibly amenable to surgical treatment. The count was found to be 3,000 per cubic millimeter, and the cells were said to be all lymphocytes. The patient died after receiving a total amount of novaldin of about 7 Gm.

Acute agranulocytosis which developed during a course of antisyphilitic treatment with neoarsphenamine and bismuth is reported by McGibbon and Glyn-Hughes.[242] It is ascribed to the toxic effect of the arsenical drug on the leukopoietic tissues. The patient had fever, sore throat and a total white blood cell count of 3,000 per cubic millimeter with 2,270 small mononuclears, 120 large mononuclears and 600 polymorphonuclears per cubic millimeter. It is obvious that the patient had the clinical picture of agranulocytosis, but there is no statement concerning the hemoglobin level, the red blood cell count or the number of platelets in the circulating blood. It is conceivable, but unlikely, that the patient may have had aplastic anemia. The fact that recovery followed the administration of pentnucleotide solution, that there were no hemorrhagic manifestations and that there is no mention of pallor would indicate that the diagnosis was probably one of agranulocytosis. The authors recommend, on the basis of their experience, that white blood cell counts should be made for all patients in whom sore throat develops during arsenical treatment. They also suggest that agranulocytosis in patients undergoing treatment with one of the arsphenamines need not be a contraindication to the subsequent use of mapharsen if a careful watch is kept on the leukocyte level.

The use of sulfapyridine is recommended by Heilig and Visveswar [243] for the treatment of

237. Heldt, T. J., and Goder, G. A.: Agranulocytosis Following Malarial Therapy in General Paresis, J. Nerv. & Ment. Dis. **98**:248, 1943.

238. Meyer, A.: Agranulozytose nach Impfmalaria, Deutsche med. Wchnschr. **57**:226, 1931.

239. Jacobson, E., and Abel, W.: Agranulozytose nach Impfmalaria, Deutsche med. Wchnschr. **59**:371, 1933.

240. Moore, J. E.: The Modern Treatment of Syphilis, Springfield, Ill., Charles C Thomas, Publisher, 1938.

241. Moloney, W., and Vidoli, M.: Agranulocytosis Following the Use of Novaldin: Report of Case, Am. J. Clin. Path. **13**:317, 1943.

242. McGibbon, C., and Glyn-Hughes, F.: Secondary Agranulocytic Angina, Lancet **1**:173, 1943.

243. Heilig, R., and Visveswar, S. K.: Malignant Leukopenia Successfully Treated with Sulfapyridine, J. A. M. A. **122**:591 (June 26) 1943.

highly toxic infections of the urinary tract even in the presence of granulocytopenia. In 2 cases reported the total doses of the drug, given with alleged beneficial results, were 6.25 and 10.25 Gm. This paper emphasizes what has previously been observed in this country, namely, that leukopenia is not necessarily a contraindication to the use of a sulfonamide drug unless the particular drug administered has been responsible for the leukopenic condition.

The case of a 20 year old woman who was known to have suffered from agranulocytosis for four years is reported by Shallard.[244] The patient was admitted to the hospital for attacks of abdominal pain which led to appendectomy. On her admission the white blood cell count was 3,100 per cubic millimeter with 13 per cent polymorphonuclear cells. There was no change in the number of granulocytes after thirteen intramuscular injections of pentnucleotide solution and a transfusion of 500 cc. of blood. Appendectomy was performed without difficulty. After an interval of three and a half years the white blood cell count was 2,600 per cubic millimeter with 34 per cent neutrophils. Despite the leukopenia, the patient has suffered no illness apart from two pustules in the axilla. The possibility of hypersplenism was considered as an explanation of the condition, but the patient refused to have a biopsy of bone marrow in order to determine the presence or absence of hyperplasia of the marrow.

A patient presenting an interesting example of granulocytopenia with severe anemia and staphylococcemia was observed by Hawkinson and Kerr.[245] The possibility must be considered that this patient did not have a true agranulocytosis because of the associated anemia. Diagnoses of aplastic anemia and subleukemic lymphatic leukemia received consideration. It would seem likely that either of these conditions may have been responsible for the patient's clinical picture, although the necropsy observations were equivocal. The author states that there did not appear to be any etiologic factor except possibly acetylsalicylic acid, which had been taken daily in a dose of 2.7 to 4 Gm. over a period of years. We cannot agree that this drug, in any dose, has been proved to be the cause of a blood dyscrasia resembling that reported in this communication.

244. Shallard, B. T.: Granulocytopenia, M. J. Australia **2**:257, 1943.

245. Hawkinson, O., and Kerr, E. K.: Case of Granulocytopenia with Severe Anemia and Staphylococcemia, Where the Only Etiological Factor Was Use of Aspirin in 40-60 Grain Doses Daily for Years, Illinois M. J. **83**:168, 1943.

The diagnosis and nature of panleukopenia (agranulocytosis) in the cat is discussed by Riser.[246] He states that this condition was considered for many years to be infectious feline enteritis and was thought to be a specific disease of the digestive tract. Recent investigations have shown, however, that it is not a primary intestinal infection but is a virus disease characterized by panleukopenia. The one important change that occurs in panleukopenia is the decrease in white blood cells of the peripheral blood. This pathologic change is constant and is to be emphasized as a diagnostic criterion. Young kittens are the most susceptible to the infection, as older cats acquire an immunity by exposure. Immunologically, recovery from one attack of the disease confers a permanent immunity on the animal. So far, the virus of panleukopenia has been found to cause infection only in the domestic cat.

Treatment.—The briefly reported experiments of Axelrod, Gross, Bosse and Swingle[247] are of unusual importance, because they confirm the previous findings that the leukopenia and agranulocytosis which develop in rats receiving sulfaguanidine in purified diets can be prevented or cured by the adminsitration of either liver or the norite eluate of liver. Their experiments show that in each instance the granulocytes are greatly reduced after the administration of a purified diet plus sulfaguanidine. With the addition of either liver or liver eluate to the diet of these animals, there was a striking increase in the number of circulating granulocytes, sometimes within forty-eight hours after the liver or eluate was given. They also noted that with the administration of paraaminobenzoic acid there was a moderate but variable increase in the number of circulating leukocytes. They conclude that the available evidence strongly favors the view that sulfaguanidine functions through its ability to inhibit the synthesis of factors by intestinal bacteria. If such is the case, it is apparent that the norite eluate fraction contains one or more factors essential to the normal functioning of the hemopoietic tissue in the rat.

In accord with the observations just cited is the work of Daft and Sebrell,[248] who observed

246. Riser, W. H.: The Diagnosis of Panleucopenia (Agranulocytosis) in the Cat, Michigan State Coll. Vet. **3**:131, 1943.

247. Axelrod, A. E.; Gross, P.; Bosse, M. D., and Swingle, K. F.: Treatment of Leucopenia and Granulopenia in Rats Receiving Sulfaguanidine in Purified Diets, J. Biol. Chem. **148**:721, 1943.

248. Daft, F. S., and Sebrell, W. H.: The Successful Treatment of Granulocytopenia and Leukopenia in Rats with Crystalline Folic Acid, Pub. Health Rep. **58**:1542, 1943.

that three solutions of crystalline folic acid furnished from two different sources showed activity in correcting leukopenia in rats induced by feeding sulfaguanidine or sulfasuxidine in purified diets. The same authors have investigated the activity of xanthopterin against granulocytopenia and leukopenia induced by sulfaguanidine and sulfasuxidine and found that it did not correct these conditions. The successful treatment of leukopenia due to sulfonamide compounds in rats with xanthopterin had been asserted by Totter and Day [249] and denied by Axelrod and his associates [247] and by Wright and Welch.[250] The experiments by Daft and Sebrell showed that when xanthopterin is given to rats with agranulopenia due to a sulfonamide drug in doses of 20 to 40 mg. daily for four successive days there was no appreciable change in the leukocyte level. All the samples of crystalline folic acid tested showed definite activity, as evidenced by an increase in the total leukocytes, and in the percentage of granulocytes. As an example of this action, the administration of one solution in a daily dose of 20 mg. of crystalline folic acid for four days was accompanied by an average increase in the total leukocytes from 2,700 to 14,400 per cubic millimeter, and in the percentage of granulocytes from 1 to 39. There was evidence indicating the probability that folic acid also possesses antianemia activity.

Ruskin's [251] report is concerned with the study of the lesions of the mucous membranes that are pronounced in the diseases characterized by leukopenia and manifested in the extreme by agranulocytosis, and with the role of the nucleotides in therapy. In his opinion, extensive physiologic investigation of adenylic acid nucleotide has shown, among other things, that its administration is followed by elevation of the entire blood picture, with simultaneous increases in the hemoglobin, the red cell count and the white cell count. The author gives a prolonged consideration of the chemistry of nucleic acid and concludes, without proof convincing to us, that "in dealing with the leukopenic states we are confronted with a variety of mechanisms, bacterial toxins, therapeutic toxins, chemical and physical toxins, all of which are alike able to disturb the nucleic acid metabolism producing a closely related clinical picture. The failure, however, of nucleotide therapy in some cases indicates that other unrecognized chemical mechanisms besides that of nucleic acid may disturb the normal reaction of the mucous membranes." Four cases, 1 of agranulocytosis and 3 of leukopenia associated with therapy with sulfonamide compounds are reported in which recovery followed the intramuscular injections of a nucleotide iron adenylate. The author considers that these case reports indicate that the medication quickly corrected the leukopenia incident to the treatment with sulfonamide compounds.

Diamond [252] observed a patient with the "idiopathic" form of agranulocytosis in whom three distinct relapses or attacks occurred. He concludes, after employing a number of therapeutic agents, including blood transfusion, pentnucleotide solution, liver extract, vitamin C, sulfathiazole and yellow bone marrow concentrates, that the last named, especially in the concentrated injectable form, is the most promising of the group for the treatment of this condition. Conclusions based on the observation of a single case cannot be accepted by us as conclusive evidence of the effectiveness of this form of therapy, but its further trial is warranted.

INFECTIOUS MONONUCLEOSIS

No outstanding new facts have been reported concerning infectious mononucleosis during the year. In one paper a careful survey of a large epidemic of the disease is described. Two important points were disclosed: first, that a large number of the patients had a latent form of the disease without symptoms or signs and apparent only by examination of the blood, and, second, that two elderly women, one of 84 and the other of 64 years, had the condition, which is unusual, as it is most frequently observed in children or young adults. A comprehensive review of the relation of the organism Listerella monocytogenes to the malady is given. A case of special importance, illustrating the association of infectious mononucleosis with the Guillain-Barré syndrome, is reported.

A brief review of the development of knowledge concerning infectious mononucleosis is given by Sokal,[253] and the general problem of this disease is presented from the practitioner's standpoint, since, according to the author, it is he who usually sees the patient first. He states

249. Totter, J. R., and Day, P. L.: Xanthopterin in the Treatment of Leucopenia and Weight Loss in Rats Fed Succinylsulfathiazole, J. Biol. Chem. **147**: 257, 1943.

250. Wright, L. D., and Welch, A. D.: The Production of Folic Acid by Rat Liver in Vitro, Science **98**:179, 1943.

251. Ruskin, S. L.: Adenylic Acid in the Treatment of Agranulocytosis and Mucous Membrane Lesions: "Some Biochemical Aspects of Leukopenia," Am. J. Digest Dis. **10**:81, 1943.

252. Diamond, J. L.: Idiopathic Agranulocytosis with Particular Reference to Treatment, M. Bull. Vet. Admin. **19**:424, 1943.

253. Sokal, H. B.: Infectious Mononucleosis, from Point of View of General Practitioner, New York State J. Med. **43**:848, 1943.

that the diagnosis is now based on three essential factors: (1) the findings in the blood, (2) the serologic reaction and (3) the clinical picture. He considers that the presence of the characteristic mononuclear cells is the most constant and therefore the most useful diagnostic sign of the disease. The heterophile antibody reaction, which must be positive in a minimum titer of 1:64 in order to be of diagnostic significance, usually reaches that level in the first week. The author states that for the present it is safer to regard only positive reactions as of diagnostic value. A negative heterophile antibody reaction does not necessarily exclude the possibility of infectious mononucleosis. In addition to the classic clinical picture, various other types are mentioned, as follows: the type in which the glands are not enlarged or are enlarged only slightly; the type with a cutaneous exanthem, which may resemble the rash of German measles or of any of the acute exanthematous infectious diseases; the abdominal type, which may resemble acute appendicitis; the meningeal and cerebral varieties; the common respiratory type, and, finally, the asymptomatic type. In the author's opinion, the last form, which is manifested only by the presence of the characteristic blood picture, should be interpreted as evidence that the disease has occurred in the past rather than as an indication of an active infection.

Houser [254] gives a general review of the symptomatology of infectious mononucleosis and considers the various forms of treatment which have been used for the condition. He emphasizes that one should suspect all cases of sore throat that continue ten days or longer and apply proper tests to confirm or disprove the presence of the disease. He mentions treatment with sulfathiazole, bismuth potassium tartrate and scarlet fever convalescent serum, but concludes that "the treatment of this condition leaves much to be desired."

In August 1942, Halcrow, Owen and Rodger [255] observed an epidemic of infectious mononucleosis in an Emergency Medical Service hospital in England, which they studied with great care and reported in detail. Most of the patients were between the ages of 20 and 45 years, but 2 older patients of uncommon interest were observed. One was a woman of 84 years who had no clinical manifestations of the disease but whose blood gave a positive Paul-Bunnell reaction in a dilution of 1:128 and showed mononucleosis, with a monocyte count of 65 per cent. The other was a woman of 64 years who had no symptoms or signs of the disorder and a negative reaction to a sheep cell agglutination test but whose blood revealed the typical picture of the disease. The average incubation period for their patients varied between five and ten days. The total number of persons examined for evidences of the disease included 273 hospital inmates and 23 members of the nursing and medical staffs. It was found that 97.9 per cent of the persons examined showed evidence of the disorder. Of these, 125 had clinical signs of the malady and 165 had no complaints or physical abnormalities but had the characteristic lymphocytes in the peripheral blood and the serologic changes typical of the condition. In the latter group the condition could not have been detected without special studies on the blood. These latent forms of the disease were one of the most remarkable aspects of the epidemic. The authors explain them on the theory that the patients' immunity was great enough to prevent the onset of the clinical manifestations, as in carriers of diphtheria bacilli and meningococci. They state, however, that in infectious mononucleosis the presence of the infecting virus produces changes in the blood picture and stimulates the production of the heterophile antibodies, and hence latent forms are easily detected. In only 6 persons of the 296 examined could the disease be excluded. In no previous epidemic, according to the authors, has there been such a high percentage of latent infections. There was nothing especially unusual about the clinical picture of the condition as it was observed in this epidemic. In nearly all of the cases the peripheral lymph glands were enlarged and tender. Intrathoracic pain was common and often suggested the presence of a beginning pneumonia. Headache, fever, malaise and sore throat were frequent manifestations, and meningeal symptoms, cutaneous eruptions of various kinds and abdominal complaints were present in about the same percentage encountered in other epidemics of the disease. Jaundice was not observed. The spleen was enlarged in about 10 per cent of the cases, which is a rather low incidence. In 1 case the edge of the spleen extended below the umbilicus, which is an unusual degree of enlargement in our experience. It is also of interest to note that although the Wassermann, Kahn and flocculation tests were done in many cases, the reactions were found to be consistently negative irrespective of the titer of the Paul-Bunnell reaction. This varies from the usual experience that the serologic tests for syphilis elicit positive reactions in about 10 per cent or more of cases

254. Houser, K. M.: Infectious Mononucleosis, Pennsylvania M. J. **46**:1173, 1943.

255. Halcrow, J. P. A.; Owen, L. M., and Rodger, N. O.: Infectious Mononucleosis, with an Account of an Epidemic in an Emergency Medical Service Hospital, Brit. M. J. **2**:443, 1943.

of infectious mononucleosis. The incidence of positive reactions would probably be higher in this series if the blood had been tested at more frequent intervals. Of the 296 persons examined, 202, or 68 per cent, had a positive Paul-Bunnell reaction in a titer of 1:64 or higher, which the authors regard as diagnostic of the disease. A positive reaction in a titer of 1:32 they consider as suggestive and a finding which demands a repetition of the test within a few days. They did observe a few patients in whom a positive reaction in a dilution of 1:32 was noted early in the course of the disease but later the reaction became positive in higher diagnostic titers. The changes in the blood observed were similar to those commonly seen. The total white blood cell count varied between 8,000 and 20,000 per cubic millimeter, but rarely did it reach the latter figure. The most striking change was the almost complete disappearance of the small lymphocytes which occurred early in the course of the disease. With this there was a great increase in the number of characteristic abnormal lymphocytes. Other changes observed were a shift to the left in the polymorphonuclear cells and the presence in their cytoplasm of basophilic granulations. Early in the disease the eosinophils were absent, but later in the course they returned in numbers greater than normal. An unusual feature was the increase in basophils to 1 to 3 per cent which occurred in the blood of many of the patients in the beginning phase of the disease. The alterations in the blood usually persisted for several weeks, but in a fair proportion of cases abnormal cells could be detected in the circulating blood for as long as three months. No new information was added concerning treatment of the condition. It was emphasized that the disorder often presents a problem in differential diagnosis, as it may be confused with the following diseases: diphtheria, septic meningitis, catarrhal jaundice, atypical pneumonia, agranulocytosis, secondary syphilis, rubella, erythema nodosum, typhoid and leukemia. They conclude, wisely, that the diagnosis of infectious mononucleosis should not be made on any one test but that the Paul-Bunnell reaction, the hematologic findings and the clinical manifestations should all be correlated before one comes to a decision.

A series of 131 patients with infectious mononucleosis, including the patients and staff of a hospital and the family of a medical officer, were investigated by Stevenson and Brown.[256] These patients were grouped into three divisions, as follows: (*a*) 14 patients showing the classic syndrome of infectious mononucleosis; (*b*) 20 patients with acute illnesses for which alternative diagnoses were made; (*c*) a group of 89 persons with subclinical forms, 73 having symptoms only of their original illness, for instance, fracture or peptic ulcer, and 16 members of the staff who were asymptomatic. A detailed report of the clinical manifestations is given, which in no way differs from other accounts of the disease. Oropharyngeal signs were common and characteristic. Glandular involvement was present in a majority of cases. It was emphasized that the infection can manifest itself differently in different hosts and hence may lead to erroneous diagnoses. Of the 131 persons examined, it was found that all but 8 had features of the disease. It is surprising to us that examination of the serum of the 123 persons confirmed the diagnosis in only 21 cases. The authors suggest that if the sheep cell agglutination test had been performed later in the disease a higher incidence of positive results might have been obtained. They employed the technic of Davidsohn. Any serum showing the presence of agglutinins was tested for absorption of antibody with guinea pig kidney and beef cells, by using autoclaved emulsions prepared according to the recommendations of Barrett and retitrating with sheep erythrocytes. A true response to the antigen of infectious mononucleosis is shown by the failure of guinea pig kidney to absorb the antibody, while ox cells do so. Hematologic changes highly suggestive of the condition was the most constant finding, as in 110 of the 123 patients these were characteristic. It is the opinion of the authors that a general serologic survey of the community would not give an indication of the incidence of the infection among the public but that hematologic evidence of this disease would be present in many unsuspected persons.

Stiefel [257] studied 78 cases of infectious mononucleosis in adults (49 males and 29 females). The clinical symptoms consisted of manifestations of infection of the mouth and throat in 63, splenomegaly and lymphadenopathy in 5, meningeal irritation in 5, icterus in 2 and bronchitis, enterocolitis and urticaria each in a single patient. Spinal fluid abnormalities were encountered in 12 patients. The importance of the characteristic lymphocytes in this disease is stressed. The highest absolute lymphocyte count observed was 32,000 per cubic millimeter. Sternal punctures were performed in 29 cases, and 20 showed increased numbers of lympho-

256. Stevenson, E. M. K., and Brown, T. G.: Infectious Mononucleosis: Preliminary Investigation of a Series of Cases, Glasgow M. J. **22**:139, 1943.

257. Stiefel, H.: Zur Frage der Mononucleosis infectiosa beim Erwachsenen: An Hand von 78 Sporadischen Fällen, Foliahaemat. **67**:61, 1943.

cytic elements, reaching 40 per cent of the nucleated cells in 4 cases. The differential diagnosis was noted as difficult, with granulocytopenia, miliary tuberculosis, meningitis, catarrhal icterus and rubeola to be considered.

Prado [258] reports 12 cases of infectious mononucleosis observed as part of an epidemic starting in mid-February and declining in May. The ages of the patients ranged from 5 to 19 years.

The almost unlimited nature of the bizarre manifestations exhibited by patients with infectious mononucleosis is commented on by Pearman and Brumm.[259] They emphasize, properly, that if every patient with fever were examined carefully for lymphadenopathy and enlargement of the spleen and a differential white blood cell count were done, the diagnosis of the disease would be made more frequently. They report a typical syndrome in a 19 year old youth whose heterophile antibody reaction was negative in all dilutions greater than 1 to 10, but they state that the reaction is specific for the disease and is positive in about 90 per cent of the cases.

The protean manifestations of infectious mononucleosis are emphasized by Rinzler and Hertz,[260] and a case is reported in which there were chills and an unusual temperature reaction. The patient, a white man aged 25, had five severe chills with subsequent rises in temperature to between 101 and 104 F. from the tenth to the twenty-second day of his illness. This presented a difficult diagnostic problem, as the only other abnormal sign present during this interval was enlarged cervical glands. The reaction to the sheep cell agglutination test did not become positive until later, when for the first time the characteristic abnormal lymphocytes appeared in the circulating blood.

A fatal case of monocytic gangrenous angina is reported by Leunda, Blanco and Raggio,[261] but we insist that this should not be confused with the syndrome which is regarded in the United States as infectious mononucleosis, although the authors consider that the patient did have that condition. They base their diagnosis on the clinical picture, the positive reaction to the Paul-Bunnell test in a dilution of 1 to 128 and the blood picture. There were 3,850,000 red blood cells per cubic millimeter, 65 per cent hemoglobin and 19,200 white blood cells per cubic millimeter, with neutrophils 55 per cent, monocytes 21 per cent and lymphocytes 24 per cent. They considered that the rise in monocytes was characteristic of infectious mononucleosis. It is emphasized by them that some patients may succumb to infectious mononucleosis, but we are not in accord with this. In all cases of death claimed to be due to this condition, which is ordinarily considered to be a nonfatal one, there should be the suspicion that the patient really was suffering from some variety of acute leukemia, usually the lymphatic or the monocytic type.

Claveaux, Canzani and Salveraglio [262] observed a patient wtih infectious mononucleosis who subsequently died of agranulocytosis. They considered that the interval between the two diseases was sufficient to permit the establishment of both diagnoses. The importance of the differential diagnosis between the two conditions is emphasized, and great stress is placed on the findings in the marrow, obtained by sternal puncture. Another point emphasized in the differential diagnosis between the two diseases is that in infectious mononucleosis the lymph nodes show enlargement in places remote from the focal infection of the throat. It is possible, in our opinion, that the findings in this case may be explained on the basis of monocytic leukemia with the subsequent development of an acute subleukemic phase.

The relation of Listeria to certain types of human meningitis, meningoencephalitis and infectious mononucleosis is discussed by Webb.[263] An excellent review is given of the natural history of the disease in animals caused by Listeria ("listerosis") and the cultural and biologic tests for this organism, including the appearance of the lesions in experimental animals. Of special interest is a review of the agents, including L. monocytogenes, which have been thought to have a causative relationship to infectious mononucleosis. Bland [264] concluded that a protozoan, Toxoplasma, was the cause of the disease, since it was found in the spleens of rabbits inoculated with blood of patients with infectious mononucleosis, and these animals had a leukopenia with a

258. Prado, C.: Mononucleose infectuosa, Pediat. prát., São Paulo **15**:183, 1942.

259. Pearman, R. O., and Brumm, H. J.: Infectious Mononucleosis: Report of a Seronegative Case, J. Missouri M. A. **40**:41, 1943.

260. Rinzler, S. H., and Hertz, J. J.: An Unusual Temperature Course in Infectious Mononucleosis, J. Lab. & Clin. Med. **28**:1445, 1943.

261. Leunda, J. J.; Panizza Blanco, A., and Raggio, O. V.: Angina gangrenosa monocitica mortal, Arch. argent. de pediat. **19**:461, 1943.

262. Claveaux, E.; Canzani, R., and Salveraglio, F.: Mononucleosis infecciosa seguida de agranulocitosis aguda con gran monocitosis sanguínea; la llamada "angina a monocitos," Arch. urug. de med., cir. y especialid. **22**:136, 1943.

263. Webb, R. A.: Listeria Monocytogenes Isolated from a Case of Infectious Mononucleosis, Lancet **2**:5, 1943.

264. Bland, J. O. W.: Glandular Fever: Experimental Investigation, Lancet **2**:521, 1930; Glandular Fever: Protozoal Nature of Experimental Disease, Brit. J. Exper. Path. **12**:311, 1931.

relative mononucleosis. Van den Berghe and Liessens [265] and Van den Berghe, Liessens and Kovacs [266] suggest a virus origin of the condition. These workers, in Belgium, injected blood of a patient with infectious mononucleosis into a monkey and produced a febrile disease with leukopenia, a relative mononucleosis and a high Paul-Bunnell titer in the serum. The condition was transmitted through serial passage to other monkeys by the injection of red blood taken at the height of the fever which was passed through a Seitz filter. Wising [267] likewise suggests a virus origin and is not in accord with the view that L. monocytogenes can cause the disease. He was able to produce the typical disease in a human subject by the injection of whole unfiltered blood. Monkeys inoculated in a similar manner gave generally negative results. Nyfeldt,[268] of Copenhagen, in March 1939 first reported the successful isolation of Bacterium monocytogenes from the blood of a patient with typical infectious mononucleosis. A similar observation was made by Pons and Julianelle [269] in 1939. Webb [263] now reports the third observation of this nature. It is his opinion that the isolation of Listeria from patients with true infectious mononucleosis will become more frequent with intensive study. He admits, however, that the absence of agglutinins for this organism in the blood of some patients with the disease is definite evidence against Listeria as a cause of the condition in these cases. Moreover, Kolmer [270] has demonstrated that it is not possible to produce positive reactions to Paul-Bunnell tests in rabbits inoculated with cultures of Listeria.

Attention is directed to the association of infectious neuronitis with infectious mononucleosis by Hiller and Fox.[271] They report the case of a white girl of 17 years who was first seen by a surgeon because of pain in the upper left quadrant of the abdomen and vomiting. When enlargement of the cervical, axillary and inguinal glands and the spleen, with lymphocytosis, was found, the diagnosis of infectious mononucleosis was suggested. This was confirmed by a positive heterophile antibody reaction in a dilution of 1 : 125. The subsequent development of motor paralysis of the lower extremities of an ascending character with an accompanying involvement of the facial nerve and a cellular hyperalbuminosis of the spinal fluid satisfied the diagnostic criteria for infectious neuronitis. The entire picture, according to the authors, can be explained on the basis of infectious mononucleosis complicated by the Guillain-Barré syndrome. They emphasize that in most cases infectious neuronitis has occurred as a sequel of an infection of the upper respiratory tract. They mention, however, that there is always a possibility that an infectious neuronitis may complicate many other virus infections. They suggest that all patients with infectious neuronitis should receive a heterophile antibody test.

In reply to questions concerning therapy and infectivity of infectious mononucleosis in the notes and queries in the *Practitioner,* Tidy [272] states that there is no specific treatment for the condition. Although good results have been claimed for many therapeutic measures, it has not been demonstrated that any of them shorten the natural course of the disease. He warns against the use of sulfonamide compounds, because "the blood forming tissues are in a highly sensitive state . . . and the number of leukocytes may vary rapidly." He claims that even in moderate doses sulfonamide compounds may cause leukopenia. According to him, injection of convalescent serum involves the risk of subsequent attacks of jaundice. In answer to the question, "How long is the condition considered infectious?" Tidy's reply is that there is no evidence that infectivity is prolonged, and he states that isolation is unnecessary after the main mass of glands has subsided for one week and the temperature has become normal. He does not believe that there is evidence of infectivity during the recrudescences which occur.

265. van den Berghe, L., and Liessens, P.: Transmission de la mononucléose infectieuse humaine (fièvre ganglionnaire de Pfeiffer) au Macacus rhesus et passages successifs d'un virus filtrant, Compt. rend. Soc. de biol. **130**:279, 1939; Transmission de la mononucléose infectieuse humaine au Macacus rhesus: Résistance du virus aux basses températures, ibid. **132**:90, 1939.

266. van den Berghe, L.; Liessens, P., and Kovacs, L.: Transmission de la mononucléose infectieuse humaine au Macacus rhesus: Culture du virus en tissu, Compt. rend. Soc. de biol. **131**:156, 1939.

267. Wising, J. P.: Some Experiments with Lymph Gland Material from Cases of Infectious Mononucleosis, Acta med. Scandinav. **98**:328, 1939.

268. Nyfeldt, A.: Etiologie de la mononucléose, Compt. rend. Soc. de biol. **101**:590, 1939; Klinische und experimentelle Untersuchungen über die Mononucleosis infectiosa, Folia haemat. **47**:1, 1932.

269. Pons, C. A., and Julianelle, L. A.: Isolation of Listerella Monocytogenes from Infectious Mononucleosis, Proc. Soc. Exper. Biol. & Med. **40**:360, 1939.

270. Kolmer, J. A.: Listerella Monocytogenes in Relation to Wassermann and Flocculation-Reactions in Normal Rabbits, Proc. Soc. Exper. Biol. & Med. **42**: 183, 1939.

271. Hiller, R. I., and Fox, M. J.: Infectious Neuronitis Associated with Infectious Mononucleosis, Marquette M. Rev. **7**:152, 1943.

272. Tidy, H.: Glandular Fever, Practitioner **151**: 249, 1943.

A case of infectious lymphocytosis with evidence of possible involvement of the nervous system is reported by Duncan.[273] The author recalls that Smith[274] in 1941 described 2 cases of a condition which he designated as acute infectious lymphocytosis in which the chief diagnostic feature was an increase in the small mature lymphocytes of the circulating blood. The condition was detected fortuitously, as there were no symptoms or signs present. Differentiation from infectious mononucleosis, acute lymphatic leukemia and leukemoid reactions is necessary. In the patient reported on by Duncan, however, there was a dramatic onset with symptoms suggestive of an acute condition in the abdomen requiring surgical intervention. It was found that this patient's white blood cell count was 45,600 per cubic millimeter with 65 per cent lymphocytes. The abdominal pain was assumed to be on the basis of hyperplasia of the mesenteric lymph nodes. Within the first few days after admission to the hospital the patient complained of headache and had projectile vomiting. The acute phase of the disease lasted for only about a week, but convalescence continued for almost three months. An irregular fever occurred during the first week, reaching its peak of 103 F. on the fourth day. Throughout the rest of the course of the disease the patient was essentially afebrile. In the previously reported cases of infectious lymphocytosis the patients have remained afebrile throughout the course of the disease. The cause of the condition is not known, but in the opinion of the author it is most likely a virus infection.

LYMPHOMATOID DISEASES, LEUKEMIA AND RELATED DISORDERS

The lymphomas are classified by Picena[275] into the primary subdivisions of lymphadenoma, lymphadenosarcoma and lymphosarcoma, which are systemic, histologically related conditions, giant follicular lymphoma, which is not systemic, and lymphogranulomatosis, or Hodgkin's disease. Both lymphadenoma and lymphadenosarcoma may be either leukemic or aleukemic, the author employing the term aleukemic in its literal sense and not, as it is commonly misused, to indicate leukemic changes in the peripheral blood without leukocytosis. Leukemic lymphadenoma is apparently synonymous with chronic lymphocytic leukemia, whereas the aleukemic form is that originally described by Cohnheim. Lymphadenosarcoma and lymphosarcoma represent the types of lymphoma described by Sternberg and Kundrat respectively, the latter always being aleukemic.

Pathologic sections of lymph nodes obtained from 527 patients were studied by Murray and Broders.[276] One hundred nodes were removed at autopsy from 37 patients in whom there was no evidence of inflammation or neoplasm; 100 inflammatory nodes were studied, and the series also included 379 malignant nodes in which the neoplasm was primary, 9 nodes from patients with leukemia, a node from a patient with reticuloendotheliosis and a node from a patient with lymphangioendotheliosis. The data derived from this study are too extensive to permit recapitulation here, but the conclusions of the authors are of considerable importance. Wide variations were found in the ratios between the various cellular elements contained within noninflammatory and non-neoplastic lymph nodes; in such nodes secondary nodules (germ center of Flemming) may occasionally be absent, and various types of giant cells, sometimes exhibiting mitotic figures, may occur outside the secondary germ centers. Invasion of the capsule of a lymph node by mature lymphocytes bears no definite relation to any malignant process. Lymph cords may be present or absent in either malignant or nonmalignant lymph nodes. Loss of structure, as produced by disappearance of follicles, cords and sinuses or flowing together of cords and sinuses or proliferation of a single cell type, points toward malignant growth. The presence in the node of genuinely pathologic mitotic figures is an almost certain indication of the presence of cancer. The histologic grade of malignancy in primary lymphosarcoma, exclusive of Hodgkin's disease, bears a definite relation to the time of survival following histologic diagnosis. The survival rate for lymphosarcoma of grade I, again exclusive of Hodgkin's disease, is about the same as for giant follicular lymphoblastoma. The histologic grade of malignancy in lymphosarcoma of the Hodgkin type bears no definite relationship to the time of survival. In Hodgkin's disease the survival rate is about the same for all grades of histologic change.

Material obtained by puncture and aspiration of lymph nodes was examined by Pio da Silva,[277] and the observations were compared with those derived from the study of histologic sections of

273. Duncan, P. A.: Acute Infectious Lymphocytosis, Am. J. Dis. Child. **66**:267 (Sept.) 1943.

274. Smith, C. H.: Infectious Lymphocytosis, Am. J. Dis. Child. **62**:231 (Aug.) 1941.

275. Picena, J. P.: Las linfomatosis, Rev. méd. de Rosario **33**:528, 1943.

276. Murray, N. A., and Broders, A. C.: Pathology of Lymph Nodes: Diagnosis and Prognosis, Am. J. Clin. Path. **13**:450, 1943.

277. Pio da Silva, M.: Contribuição para o estudo da punção ganglionar como meio semiótico, Arq. de cir. clín. e exper. **7**:69, 1943.

the same tissues. Twenty-nine cases, including instances of various types of pathologic enlargement of lymph nodes, comprised the series. In 7 of 12 cases of tuberculous adenitis the correct diagnosis was made by the finding either of tubercle bacilli or of typical epithelioid and giant cells in material obtained by lymph node puncture. The etiologic agent was found in each of 8 cases of blastomycosis. In 4 cases of metastatic carcinoma a correct diagnosis was made, based on the observation of neoplastic cells in the punctate. In 2 cases of Hodgkin's disease Reed-Sternberg cells and numerous eosinophils were present in the aspirated material.

Hodgkin's Disease.—A classification, based on pathologic criteria, of 225 cases of Hodgkin's disease in which the diagnosis was verified by histologic examination is presented by Bersack.[278] The condition in group I is designated as Hodgkin's lymphoreticuloma, either typical or atypical, and is characterized by reticulum cell hyperplasia, frequent mitosis and the presence of large or medium-sized lymphocytes. Sternberg and Reed giant cells may be scarce or entirely absent. The form of the disease in group II is termed Hodgkin's granuloma, and the bulk of the cases in the series are included within this group. The typical features are pleomorphism and the presence of Sternberg and Reed cells, which the author insists are morphologically dissimilar, together with a moderate degree of fibrosis. The cases of group III are instances of what is called Hodgkin's lymphoma. This condition presents destruction of nodal architecture, only a slight tendency to pleomorphism and persistence or even prevalence of lymphocytes, which are mostly small. Few mitoses are evident, and Sternberg and Reed cells may be absent. Biopsies of lymph nodes in 11 cases of Hodgkin's disease revealed large mononucleate or binucleate cells with plasma-like nuclei. This finding, together with the appearance of mitotic figures in reticuloendothelial cells, supports, in the author's opinion, the conception of Hodgkin's disease as being of neoplastic origin.

A discussion of the reticuloendothelial system is presented by Letulle[279] with particular reference to monocytosis, monocytic leukemia and Hodgkin's disease. These conditions, he believes, all represent hyperplastic reactions of the reticuloendothelial system which may be either irritative or neoplastic. The pathogenesis of Hodgkin's disease is also discussed by Arriagada Seguel,[280] with consideration of the theories of infectious or neoplastic origin. This author lists the conditions which must be differentiated from Hodgkin's disease, considers the variable prognosis of the condition and submits his views regarding treatment by irradiation or by surgical excision of affected nodes. Cárdenas Pupo[281] emphasizes the presence in some cases of Hodgkin's disease of large phagocytic reticuloendothelial cells lying between islands of lymph cells and connective tissue.

Medinger and Craver[282] treated 94 unselected patients with Hodgkin's disease with both localized and total body irradiation. Thirty-two per cent survived five years from the onset of this disease. The median survival of the series was forty-four months, and the average survival of 75 patients who had died was forty-four and four-tenths months. Of 19 patients who were living ninety-four months or more after the development of Hodgkin's disease, the median survival was one hundred and two and five-tenths months. The disease in this series of patients was, for the most part, probably more advanced than in others reported on. One sixth of the group died within six months after their first observation.

Steiner[283] describes involvement of bone and bone marrow in Hodgkin's disease and states that the lesions, regardless of their genesis, whether arising by invasion or by extension and whether hematogenous or primary, may be osteolytic, osteogenic or mixed. He found lymphogranulomatous foci in one or more sections of bone marrow from 11 of 14 patients with Hodgkin's disease seen consecutively. They were found in 38 of the 62 sections examined. He believes that in practically every case of Hodgkin's disease lesions of the marrow would be found if enough bones could be examined thoroughly. These widespread and obscure lesions may be responsible for the pain so often experienced in this disease. In most cases, however, they are not sufficiently disseminated to account for the anemia on a replacement basis. Because such foci are scattered and adherent to bone, aspiration of marrow is not likely to provide

278. Bersack, S. R.: Hodgkin's Disease: A Pathologic Classification, Am. J. Clin. Path. **13**:253, 1943.

279. Letulle, R.: La monocytose sanguene traduit une réaction du système réticulo-endothelial, Presse méd. **51**:276, 1943.

280. Arriagada Seguel, P.: Enfermedad de Hodgkin, Rev. chilena de pediat. **14**:27, 1943.

281. Cárdenas Pupo, M. D.: Sobre los macrofagos en la enfermedad de Hodgkin, Arch. cubanos cancerol. **2**:21, 1943.

282. Medinger, F. G., and Craver, L. F.: Total Body Irradiation with Review of Cases, Am. J. Roentgenol. **48**:651, 1942.

283. Steiner, P. E.: Hodgkin's Disease: The Incidence, Distribution, Nature and Possible Significance of the Lymphogranulomatous Lesions in the Bone Marrow; a Review with Original Data, Arch. Path. **30**:627 (Dec.) 1943.

material of diagnostic value. According to the author, the distribution of the lesions in Hodgkin's disease follows the distribution of the reticuloendothelial system rather than that of the lymphatic system, and this is considered evidence that Hodgkin's disease is a disorder of the reticuloendothelial system, A case report of the Massachusetts General Hospital [284] is concerned with a man aged 58 who died of Hodgkin's sarcoma. The bone marrow was more extensively involved than any other tissue.

Busman and Johnston [285] report 37 cases of Hodgkin's disease encountered among 40,000 general admissions to the hospital. In 32 of the cases the diagnosis was confirmed by histologic examination. There were 27 male and 10 female patients, and the ages of 18 of the patients were between 51 and 70 years, an observation which is not in accord with the prevailing view that Hodgkin's disease is a disorder affecting predominantly young adults. Two general types of lesions of the skin were seen in the members of this series. The first were true Hodgkin tumors, often with ulceration and usually located above or near glandular masses. The second were the so-called "id" reactions, of toxic or nonspecific nature. The latter included generalized pruritus, maculopapular, urticarial, bulbous and vesicular lesions, pigmentation, dryness, hyperkeratosis and alopecia. Ronchese [286] reports the case of a man of 24 years in whose case a diagnosis of Hodgkin's disease was made by biopsy in May 1936. He remained in comparatively good health without treatment for two years, and then mediastinal involvement developed. Roentgen therapy was followed by remission, which persisted until June 1941. A generalized ichthyosiform atrophy of the skin then developed and he died in September 1942. This type of cutaneous lesion is considered as one of the many cutaneous nonspecific toxic manifestations of Hodgkin's disease.

Hodgkin s disease involving the stomach is discussed by Jungmann.[287] He reported the case of a man aged 60 with characteristic roentgenologic findings and pathologic verification of this condition. At operation the stomach and the spleen were removed, and the patient died a few days later of bronchopneumonia. According to the author, a valuable diagnostic sign of Hodgkin's disease of the stomach is roentgenologic evidence of extensive ulceration of the mucosa without obliteration of peristalsis. He states that three types of Hodgkin's disease of the stomach have been described. The first is ulcerative, with multiple flat ulcerations of the mucosa. The second is tumor-like, usually localized to the prepyloric region and exhibiting filling defects and narrowing of the lumen. In the third, changes are observed which involve the whole stomach, with the appearance of polyposis.

The literature concerning involvement of the gastrointestinal tract by Hodgkin's disease is reviewed by Pusch.[288] He reports the case of a man aged 49 who had had enlarged cervical nodes for two years, treated by irradiation, when he experienced acute onset of abdominal pain and nausea. At operation perforation of the duodenum was found, attributable to infiltration by Hodgkin tissue. The patient died on the fourth postoperative day. A somewhat similar development in a woman of 29 years is reported by Badia.[289] There was a well defined mass in the left upper midportion of the abdomen on the left side. Hodgkin's disease with perforation of the jejunum was found at operation.

Malignant granulomatosis in 4 children between 3 and 8 years of age is reported by Notti, Ferrer and Grinfeld.[290] In 2 of the patients there was extensive abdominal involvement with hepatomegaly and splenomegaly and severe anemia. In 1 of these serofibrinous pleurisy developed, which was attributed to compression by mediastinal lymph nodes, and in the other acute jaundice was caused by obstruction of the hepatic and common bile ducts by pressure of enlarged lymph nodes. The duration of the disease was about two years in all of the cases, and the course was not affected by roentgen, radium, arsenic or liver therapy.

Cases of Hodgkin's disease with involvement of abdominal nodes and obstructive jaundice are reported by Ríos and Montero [291] and Patino

284. Dienalde, F. R.; Holmes, G. W., and Mallory, F. B.: Malignant Lymphoma, Hodgkin's Sarcoma Type, Involving Lymph Nodes, Spleen and Bone Marrow, New England J. Med. **227**:642, 1942.

285. Busman, G. J., and Johnston, J. M.: Hodgkin's Disease in Dermatologic and General Practice, Pennsylvania M. J. **46**:1153, 1943.

286. Ronchese, F.: Ichthyosiform Atrophy of the Skin in Hodgkin's Disease, Arch. Dermat. & Sypth. **47**:778 (June) 1943.

287. Jungmann, H.: Hodgkin's Disease of the Stomach, Brit. J. Radiol. **16**:386, 1943.

288. Pusch, L. C.: Hodgkin's Disease of the Duodenum, Pennsylvania M. J. **45**:20, 1941.

289. Badia, P. D.: Primary Hodgkin's Sarcoma of Jejunum with Perforation, Resection and Radiotherapy: Case Report, Am. J. Surg. **59**:577, 1943.

290. Notti, H. J.; Ferrer, H. V., and Grinfeld, A.: Manifestaciones poco frecuentes de la linfogranulomatosis maligna en la infancia; pleuresia serofibrinosa e ictericia por compresión ganglionar, Arch. de pediat. d. Uruguay **14**:403, 1943.

291. Ríos, E., and Montero O., E.: Ictericia obstructiva por enfermedad de Hodgkin abdominal, Rev. méd. de Chile **70**:1001, 1942.

Mayer.[292] Amyloidosis and myelophthisic anemia were observed and confirmed by necropsy in a case of Hodgkin's disease of about two years' duration reported by Lehman.[293] The case of a woman aged 27 with Hodgkin's disease of the breast is reported by Wray.[294] A male infant with generalized involvement of peripheral lymph nodes and the histologic picture of Hodgkin's disease was living ten years after the diagnosis had been made and had developed normally, according to Cervini and his associates.[295] The case of a 41 year old Mexican physician with Hodgkin's disease involving the upper mediastinum, the left lung and the bronchi is reported by Smith and Shefts.[296] They state that the ideal procedures for establishment of the diagnosis of Hodgkin's disease are laminagraphic roentgen examination, visualization of the bronchi with iodized poppyseed oil and bronchoscopy with biopsy. In this case masses of Hodgkin tissue projected into the lumen of a bronchus and simulated the appearance of carcinoma. Viets, MacMahon and Squires[297] report the case of a man, aged 43, with Hodgkin's disease in whom Schilder's disease, or encephalitis periaxialis diffusa, developed.

Lymphosarcoma.—The case histories of 47 patients with lymphosarcoma are analyzed and discussed by Howes and Levin.[298] Of this series 13 were alive from two to six years after the diagnosis was made. Nine of these had no evidence of tumor at the time of the report. Of 36 patients with the generalized form of the disease only 4 were living two to six years after the diagnosis was made. According to the authors, in the presence of evidence of metastasis the areas treated by irradiation should include the retroperitoneal and mediastinal. There is no discussion of findings in the blood in this article. Ahlström[299] discusses the incidence of reticulum cell sarcoma and states that 10 per cent of tumors of the nose and throat and 25 per cent of tumors of the tonsils are of this type. There are two such tumors on the basis of the cellular picture: In one the reticular cells are arranged in rows with a few lymphocytes present; in the other there is massive hyperplasia of the reticulum giving the appearance of carcinoma. In the spleen the same types of reticulum cell sarcoma occur as in the lymph nodes. The question of whether the spleen possesses complete blood-forming potentialities is raised. Although the same types of reticulum cell sarcoma are found in the lymph nodes, spleen, lymph tissue of the intestinal canal, throat and skeleton, special regional differences are observed. In the throat the tumors are more often of the massive type than in the lymph nodes. In sarcoma of the spleen the structural arrangement may be that of an endothelioma, which is not like that seen in lymph nodes. With skeletal reticulum cell sarcoma the prognosis is more favorable than it is with such tumors in other locations. The differences in structure and in rapidity of growth may be due to the regional environment or to characteristics of the precursor cells in the various tissues of the body subject to this type of neoplasm.

Seven cases of typical small round cell lymphosarcoma and 1 of reticulum sarcoma of the stomach are reported by Yarnis and Colp.[300] The gross appearance of lymphosarcoma of the stomach is of two kinds. In one type the cells are diffusely infiltrating, causing an apparent simple hypertrophy of the rugae, and in the other definite tumor formation may be present, often with ulcerations.

The case of a man aged 57 with primary lymphosarcoma of a tonsil and ulcerative metastasis to the greater curvature of the stomach is reported by Buschke and Cantril.[301] The lesion of the stomach disappeared after irradiation, as evidenced by both the roentgen and the gastroscopic findings, but there was progression of generalized involvement by the disease.

The case of a man aged 38 who had reticulum cell sarcoma of the spleen is reported by Haus-

292. Patino Mayer, C.: Linfogranulomatosis; perplejidades diagnósticas en el comienzo y evolución de una linfogranulomatosis abdominal, Prensa méd. argent. **30**:1641, 1943.

293. Lehman, R. G.: Hodgkin's Disease Complicated by Amyloidosis and Nephrotic Syndrome: Case Report, Ohio State M. J. **39**:232, 1943.

294. Wray, S.: Hodgkin's Disease of Breast, J. Path. & Bact. **55**:75, 1943.

295. Cervini, P. R.; di Bartolo, A., and Weber H.: Evolución favorable de un niño que tiene actualmente 10 años de edad y que presentó un linfogranuloma maligno en la época de la lactancia, Arch. argent. de pediat. **18**:121, 1942.

296. Smith, E. B., and Shefts, L. M.: Hodgkin's Disease: Report of Case with Involvement of Bronchi, J. Thoracic Surg. **12**:296, 1943.

297. Viets, H. R.; MacMahon, H. E., and Squires, G. V.: Case of Hodgkin's Disease and Schilder's Disease, Bull. New England M. Center **5**:86, 1943.

298. Howes, W. E., and Levin, B.: Lymphosarcoma: Statistical Study and Evaluation of Treatment, Radiology **40**:565, 1943.

299. Ahlström, C. G.: Zur Kenntnis der extralymphoglandulären Reticulumzellensarkome und ihrer Differentialdiagnostik, Beitr. z. path. Anat. u. z. allg. Path. **108**:169, 1943.

300. Yarnis, H., and Colp, R.: Lymphosarcoma of the Stomach, Gastroenterology **1**:1022, 1943.

301. Buschke, F., and Cantril, S. T.: Secondary Lymphosarcoma of the Stomach, Am. J. Roentgenol. **49**:450, 1943.

mann and Gaarde.[302] Splenectomy was performed with temporary improvement, but there were recurrences of the neoplasm and the patient died of the disease. The authors believe that splenectomy is indicated in cases of lymphosarcoma when the tumor appears to be confined to the spleen. A classification of malignant splenic neoplasms is given which is in accord with that of most authors, except for the inclusion in it of the lipid histiocytosis.

Lymphosarcoma arising within the skull occurred in 2 patients reported on by Abbott and Adson.[303] In the first, a man of 24 years, there was involvement of the dura mater, skull and leptomeninges. Whether the tumor arose from the skull or from the dura mater was not clear. The patient had suffered a minor injury when he was struck in the head by a baseball two years before, and it is considered possible that malignant degeneration may have occurred in a localized focus of lymphocytes. The second patient was a woman of 57 years whose symptoms began in 1925 and who died in 1932, six years after operation revealed lymphosarcoma involving the skull, dura mater, leptomeninges and brain. In this case the evidence favors but is not conclusive of origin in the dura. According to the authors, no previous cases have been reported of lymphosarcoma arising from the dura, leptomeninges or brain, nor has the skull ever been mentioned as the primary site of such tumors, although it is well recognized that lymphosarcoma may arise in bone.

According to Fritsche,[304] localized lymphosarcoma of the small intestine frequently gives rise to the sprue syndrome.

Leukemia.—A report of 123 cases of leukemia in which necropsies were performed is presented by Kirshbaum and Preuss.[305] This group constituted 0.86 per cent of 14,400 consecutive cases of autopsy at the Cook County Hospital, Chicago, between 1929 and March 1941 inclusive. The cases were classified as follows: stem cell leukemia, 28 cases, or 22 per cent of the entire series; myelogenous leukemia, 53, or 43.1 per cent; lymphatic leukemia, 37, or 30.8 per cent; monocytic leukemia, 5, or 4.1 per cent. Males made up 69.9 per cent of the patients. Stem cell leukemia occurred predominantly (69 per cent) in the first three decades of life. Grinschpun and Raventos[306] report 66 cases of chronic leukemia observed between 1931 and 1942. Of these 53 were of myeloid and 13 of lymphoid leukemia. The blood picture was leukemic in 49 and subleukemic in 4 of the cases of the myeloid type. In the group of cases of lymphoid leukemia there were 9 of the leukemic type, 3 of the subleukemic and 1 of the aleukemic. Bethell[307] analyzed the case records of 495 patients for whom the diagnosis of leukemia was made at the Simpson Memorial Institute between July 1, 1927 and Dec. 31, 1941. In many instances the films of the blood and marrow of these patients were reexamined. The cases were subdivided into three main groups, designated as instances of lymphogenous, of myelogenous and of histogenous leukemia. Lymphogenous leukemia comprises lymphocytic (chronic), lymphoblastic (acute) and lymphosarcoma cell (Sternberg's leukosarcoma) types, which together accounted for 216 cases, or 43.6 per cent of the entire series. Myelogenous leukemia is further separated into myelocytic (chronic), myeloblastic (acute) and myelomonocytic (Naegeli monocytic) types; one of these types occurred in 239 cases, or 48.3 per cent of the series. The histogenous variety, of which there were 40 cases, or 8.1 per cent, includes monocytic leukemia of the Schilling type and stem cell leukemia which cannot be classified as either myeloblastic or lymphoblastic. The results of irradiation therapy of the several types of leukemia are presented in this article, with the conclusion that the value of such treatment is limited to patients with the chronic forms of the disease. Best results were obtained in cases of myelocytic and of lymphocytic leukemia. Data are given which indicate that there may be an actual increase in the incidence of the acute forms of leukemia, particularly of the histogenous type.

The nature of the predominating cells occurring in the blood in cases of chronic small cell lymphatic leukemia is discussed by Arneth.[308]

302. Hausmann, P. F., and Gaarde, F. W.: Malignant Neoplasms of Spleen; Review of Literature and Report of Case of Primary Lymphosarcoma (Reticulum-Cell Type), Surgery **14**:246, 1943.

303. Abbott, K. H., and Adson, A. W.: Primary Intracranial Lymphosarcoma: Report of Two Cases and Review of the Literature, Arch. Surg. **47**:147 (Aug.) 1943.

304. Fritsche, R.: Syndrom von symptomatischer Sprue bei Lymphosarkomatose des Dünndarms und der mesenterialen Lymphdrüsen, Schweiz. med. Wchnschr. **73**:442, 1943.

305. Kirshbaum, J. D., and Preuss, F. S.: Leukemia: Clinical and Pathologic Study of 123 Fatal Cases in Series of 14,400 Necropsies, Arch. Int. Med. **71**:777 (June) 1943.

306. Grinschpun, S., and Raventos, E.: E studios sobre leucemias cronicas; etiopatogenia, frecuencia y diagnostico, Rev. méd. de Chile **71**:645, 1943.

307. Bethell, F. H.: Leukemia: Relative Incidence of Its Various Forms, and Their Response to Radiation Therapy, Ann. Int. Med. **18**:757, 1943.

308. Arneth, J.: Zur chronischen kleinzelligen lymphatisch-leukämischen Reaktion vom qualitativen Standpunkt aus sowie zur "Myeloblastenleukämie," Med. Klin. **38**:924, 1942.

He differentiates such cells from micromyeloblasts chiefly on the basis of the form of the nucleus, the characteristics of the nucleoli and the frequent presence in micromyeloblasts of azure granulation which exhibits a positive oxidase reaction. The author presents his views on the mechanism of development of hiatus leukemicus and on the relationship of the paramyeloblast to the myeloblast. The neoplastic and infectious theories of the causation of leukemia are reviewed by Rohr,[309] who points out that in some cases leukemia may commence as a localized tumor, such as chloroma, later metastasizing and ultimately producing the picture of generalized leukemia.

Lemos Ibáñez [310] reports results of irradiation therapy in 23 cases of chronic and in 2 cases of acute leukemia. He considers that, in general, such treatment is contraindicated for acute leukemia. Treatments were given over the spleen, lymph nodes and bones in doses of 200 roentgens for adults and 100 roentgens for adolescents. Two or three irradiations were given each week until the leukocyte count declined to 15,000 or 20,000 cells per cubic millimeter. Courses of therapy were repeated every two or three months, and treatment was discontinued if acute symptoms developed, such as high fever, hemorrhage, cardiac or renal insufficiency or infection. In cases of progressive decrease of the erythrocyte count irradiation therapy was discontinued and repeated blood transfusions were given together with administration of arsenicals, a liver and iron preparation and vitamins. When there was evidence of a refractory state of the disease following local treatments teleroentgenotherapy was given twice weekly in doses of 10 or 15 roentgens each. Patients with chronic myelogenous or lymphogenous leukemia responded well to this therapeutic regimen, with remissions of activity following each course of treatments, although the completeness and duration of remissions decreased as the disease progressed to its fatal termination. The duration of life in cases of chronic leukemia appeared to have been prolonged for three to four years by irradiation therapy. In cases of myeloid metaplasia of the spleen compensating for aplasia of the bone marrow such treatment should not be employed.

Medinger and Craver [311] treated 11 patients with chronic myelogenous leukemia and 1 patient with acute myelogenous leukemia with irradiation. The average duration of life of the patients with chronic leukemia from the onset of symptoms was twenty-eight and five-tenths months, with an average survival of eighteen and six-tenths months after the institution of therapy. The longest period of survival was forty months. In this group of patients irradiation of the entire body was not superior to local treatments. Patients in advanced stages of leukemia whose spleens were refractory to local irradiation failed to respond significantly to irradiation of the whole body. Fieschi and Kienle [312] state that after effective roentgen therapy of the spleen in cases of myelogenous leukemia the myeloid infiltration may be entirely removed, but in certain instances the spleen is not reduced in size because the fundamental structure of the organ is actually enlarged. The changes in the spleen following irradiation are dependent on the size of the individual doses and on the total amount administered. Usually, in their experience, by the use of small favorably selected doses it is possible to secure a reduction in the size of the spleen to a condition approaching normal. In cases of advanced myelogenous leukemia the use of large doses of irradiation leads to complete disappearance of parenchymal cells with persistence of histioendothelial remnants which possess a definite tendency to undergo perisinusoidal proliferation.

The treatment of leukemia and related disorders is discussed by Peake,[313] who advocates the use of irradiation except in cases of acute leukemia. Isaacs [314] reports the case of a woman of 43 years suffering with chronic myelogenous leukemia who obtained a poor result from irradiation of the whole body in spite of receiving thirteen treatments over a six week period. Subsequently she responded well to intensive local treatment over the spleen given in conjunction with blood transfusion and the administration of an arsenic preparation and a spleen extract. The patient was in apparent good health four and a half years after the onset of the disease.

The value of pyridoxine in the treatment of irradiation sickness is emphasized by Maxfield and his associates.[315] Pyridoxine hydrochloride

309. Rohr, K.: Zur Tumorlehre der Leukämien, Klin. Wchnschr. **22**:351, 1943.

310. Lemos Ibáñez, A.: Roentgenterapia de las leucemias, Semana méd. **2**:157, 1943.

311. Medinger, F. G., and Craver, L. F.: Total Body Irradiation, with Review of Cases, Am. J. Roentgenol. **48**:651, 1942.

312. Fieschi, A., and Kienle, F.: Ueber Röntgenstrahlenwirkungen auf die Milz bei myeloischer Leukämie, Ztschr. f. d. ges. exper. Med. **108**:22, 1940.

313. Peake, J. D.: Leukemias, Hodgkin's Disease and Lymphosarcoma: Brief Discussion and Treatment, J. M. A. Alabama **12**:296, 1943.

314. Isaacs, R.: Leukemia: Symptomatology and Treatment, M. Clin. North America **27**:251, 1943.

315. Maxfield, J. R., Jr.; McIlwain, A. J., and Robertson, J. E.: Radiation Sickness and Pyridoxine, Radiology **41**:383, 1943.

is given in doses of 25 mg. by intravenous injection commencing immediately after the onset of radiation sickness and repeated at intervals of twenty-four to seventy-two hours as needed. This form of treatment may be useful in the management of patients undergoing roentgen therapy for leukemia.

Good hematologic and clinical remission in a case of chronic myelogenous leukemia was obtained by Mitchell [316] with the use of potassium arsenite. He advocates initial arsenical treatment for this disease, followed in its late stages by roentgen therapy.

Amidon,[317] following the earlier work of Livingston and Moore, treated 4 patients with lymphatic leukemia with a sulfonamide preparation. In 2 of the patients there was decrease in the total leukocyte count with some clinical improvement, although in 1 of these the effects were very transient. In 2 other patients there were few or no observed results. Rhoads and Abels [318] administered avidin to 2 patients, one suffering with chronic lymphatic leukemia and the other with carcinoma of the breast. The material was given over a thirty week period in amounts from sixteen to forty times as great as those required to bind the biotin contained in the diets of the subjects. No clinical evidence of biotin deficiency was observed, nor was the urinary excretion of biotin low. There were no effects on the expected clinical course in either case.

Theories of the origin of the monocyte with particular reference to leukemia are reviewed by Strangmann,[319] who reports the case of a woman aged 37 with monocytic leukemia. When she was first observed the monocytes in the peripheral blood were predominantly young forms, but as the disease progressed they exhibited greater maturity. A similar "shift" was observed in the cells of the myeloid and lymphatic series. The author considers that these changes are of diagnostic value in cases of monocytic leukemia. Piechl [320] discusses the types of monocytic leukemia and reports 2 cases of the disease illustrating origins in the reticuloendothelial and in the myeloid system.

316. Mitchell, D.: Treatment of Chronic Myelogenous Leukemia with Arsenic, Irish J. M. Sc., 1943, no. 207, p. 91.

317. Amidon, E. L.: The Reaction of Leucemic Patients to the Sulfonamides, J. Lab. & Clin. Med. **28**: 1691, 1943.

18. Rhoads, C. P., and Abels, J. C.: Administration of Egg White and Avidin Concentrates to Patients with Cancer, J. A. M. A. **121**:1261 (April 17) 1943.

319. Strangmann, E.: Zur Frage der Monocytenleukämie, Klin. Wchnschr. **22**:12, 1943.

320. Piechl, N.: Beitrag zur Frage der Monocytenleukämie, Folia haemat. **67**:128, 1943.

Three cases of erythroleukemia are reported by Major and Weber.[321] A woman aged 31 was first seen with the blood picture of chronic myelogenous leukemia. Subsequently, after improvement following irradiation therapy, polycythemia developed. Another woman, aged 49, had similar but less pronounced changes after roentgen therapy for chronic myelogenous leukemia, with subsequent reversion to a leukemic picture with anemia. A man of 65 years had persistent slight elevation of the erythrocyte count with moderate leukocytosis and a few myelocytes and metamyelocytes in the peripheral blood. The spleen was enlarged, and blood volume was increased. Little change was noted over a two year period. Pontoni [322] discusses the usual clinical and pathologic picture of acute erythremia and compares this disorder with the acute forms of leukemia. He reports the case of a woman aged 23 in whose case the diagnosis of acute erythremia was made. The course of the disease was rapid. Detailed observations made in clinical examinations, in studies of the peripheral blood, by organ puncture and at necropsy are given. There was extensive infiltration of uniform histioblasts and erythroblasts practically replacing all other tissues in the marrow and spleen. Unusual developmental forms of the erythrocyte series, which appeared to be of direct mesenchymal origin, were observed. Immature granulocytes were also conspicuous.

Cases of leukemia cutis associated with lymphogenous leukemia are reported by Stuart,[323] whose patient, a woman of 49 years, had a nodular eruption of the forehead, nose, cheeks and front of the chest, and Gonzalez Medina,[324] who emphasizes the common occurrence of cutaneous lesions in this form of leukemia. Fuhs [325] classifies the cutaneous manifestations of leukemia into a nonspecific group, including impetigo-like, furunculous, pruritic, petechial and ecchymotic lesions, and a specific type, characterized by reddish brown knots of tumor tissue appearing on the trunk and extremities but seldom on the face in cases of chronic leukemia of both myelogenous and lymphogenous varieties.

321. Major, R. H., and Weber, C. J.: Erythroleukemia, J. Kansas M. Soc. **44**:299, 1943.

322. Pontoni, L.: Die akute erythrämische Myelose, Folia haemat. **67**:4, 1943.

323. Stuart, A. M.: Leukemia Cutis, Brit. J. Dermat. **55**:65, 1943.

324. Gonzalez Medina: Leucemia cutis de forma limfoide, Actas dermo-sif. **33**:122, 1941.

325. Fuhs, H.: Ueber Hauterscheinungen bei chronischen Leukosen und der Lymphogranulomatosis (Paltauf-Sternberg), Wien. klin. Wchnschr. **55**:121, 1942.

This distribution is in contrast to that occurring in the lymphomas. Gerbis [326] reports the case of a man of 52 years who received irradiation treatment for eczema due to turpentine and subsequently showed acute leukosis. There were myeloid changes in the bone marrow, myeloid metaplasia in the liver and spleen, hemorrhagic manifestations and pulmonary edema.

Acute lymphatic leukemia in childhood is discussed by Falkenstein and Fowler,[327] who report 61 cases in which the condition occurred in patients under 16 years of age. Subleukemic and leukemic forms of the disease were about equally prevalent, with the progress of the disease somewhat more rapid in the cases of the leukemia type. It is concluded that roentgen therapy may be of some value in the relief of pressure symptoms but that in the absence of such manifestations it is of no benefit and may be actually harmful.

The differential diagnosis of acute leukosis, infectious mononucleosis, leukemoid reactions and von Jaksch's anemia is considered by Radnay,[328] who reports 4 cases illustrating these conditions. Gill and McCall [329] report the case of a girl aged 18 in which biopsy of an enlarged lymph node revealed lymphadenoma with the presence of Sternberg-Reed cells, reticulum cell hyperplasia and many eosinophils and plasma cells. A good therapeutic result was obtained from irradiation therapy over peripheral and mediastinal areas of lymph tissue, but two years later there developed the picture of lymphogenous leukemia with many lymphoblasts in the peripheral blood.

McEntee [330] reports a case of acute lymphoblastic leukemia in a 3½ year old girl which underwent complete clinical remission after two small blood transfusions. Two months later recurrence developed, with rapid progress and death. The same author reports the case of a man of 43 years who experienced weakness and anorexia for two weeks before the development of a carbuncle for which he sought medical attention. Examination of the blood in this case revealed acute myeloblastic leukemia. A case of acute lymphogenous leukemia in which hemorrhagic manifestations predominated in a girl of 1¾ years is reported by Wolfram.[331] The case of a 23 year old woman suffering with localized lymphosarcoma who obtained a good therapeutic result from roentgen and arsenical treatment but in whom disseminated lymphosarcoma with a leukemic blood picture developed later is reported by Fuhs.[332] Gómez Camejo and Bidot Peralta [333] report a case of mycosis fungoides in a man of 23 years who after presenting a normal blood picture for two years showed progressive anemia and leukemia, probably of lymphogenous type. Rosen [334] describes an instance of Kaposi's hemorrhagic sarcoma associated with the blood picture of lymphogenous leukemia. Two cases of acute myeloid leukemia in men in which the peripheral blood presented the picture of hiatus leukemicus are reported by Della Vida and Connell.[335]

Schiller [336] discusses the two theories which may be advanced to explain extramedullary hemopoiesis in leukemia, namely, that it is due to local transformation of cells or to colonization. The first theory is more difficult to prove, but it seems probable, so far as the lymph nodes, spleen and liver are concerned, since these tissues are sites of blood formation during fetal development. Evidence in favor of this theory is provided by the observation of transformation of endothelial cells, such as Kupffer cells, into monocytes. A case is reported of a Negro woman of 46 years with chronic myelogenous leukemia in whom necropsy revealed transformation of Kupffer cells into eosinophilic myelocytes. The latter underwent development and were seen in the process of entering the blood of the hepatic sinusoids as eosinophilic granulocytes.

Between Jan. 1, 1938 and January 1942 necropsy was performed in 28 cases of leukemia

326. Gerbis, H.: Aleukämische Myelose nach therapeutischer Röntgenbestrahlung der Haut, Deutsche med. Wchnschr. **69**:540, 1943.

327. Falkenstein, D., and Fowler, W. M.: Acute Lymphatic Leukemia in Childhood, Am. J. Dis. Child. **65**:445 (March) 1943.

328. Radnay, B.: Leukämien des Säuglings und Kindesalters, Zentralbl. f. allg. Path. u. path. Anat. **80**: 409, 1943.

329. Gill, A. W., and McCall, A. J.: Lymphadenoma and Leukaemia, Brit. M. J. **1**:284, 1943.

330. McEntee, B.: Acute Leukaemia, Irish J. M. Sc., 1943, no. 213, p. 549.

331. Wolfram: Lymphatische Leukämie mit Tumorförmigen Knoten und akuten Verlauf, Wien. klin. Wchnschr. **55**:698, 1942.

332. Fuhs, H.: Aleukämische-lymphatische Tumoren mit aggressivem Wachtsum, Wien. klin. Wchnschr. **55**: 697, 1942.

333. Gómez Camejo, M., and Bidot Peralta, C.: Micosis fungoide a tumor d'emblée, que termina con un cuadro de leucemia hemocitoblástica, Rev. méd. cubana **53**:1055, 1942.

334. Rosen, I.: Idiopathic Hemorrhagic Sarcoma and Lymphatic Leukemia, Arch. Dermat. & Syph. **48**:566 (Nov.) 1943.

335. Della Vida, B. L., and Connell, M. C.: Acute Aleukaemic Myeloid Leukaemia, Brit. M. J. **2**:417, 1943.

336. Schiller, W.: Local Myelopoiesis in Myeloid Leukemia, Am. J. Path. **19**:809, 1943.

in the Chantz Hospital, New Orleans.[337] Of these, 20 cases were of the lymphogenous type, with 13 instances of chronic, 5 of subacute and 2 of acute leukemia. In 8 cases the disease was classified as myelogenous, with 4 instances of chronic, 3 of subacute and 1 of acute involvement. In 1 case of myelogenous leukemia the mucosa of the stomach and colon were involved, and in another case the gastric mucosa was extensively infiltrated by leukemic tissue without involvement of the remainder of the alimentary tract. In both of these cases there was macrocytic anemia with a high mean corpuscular hemoglobin value, an observation of interest since it suggests interference with production of the intrinsic factor.

The subject of remissions in leukemia is discussed by Moeschlin,[338] who reports a case of paramyeloblastic leukemia in which three distinct remissions, of seven, three and two months, occurred. Death ensued sixteen months after the onset of the illness. In this case sternal puncture revealed both leukemic and normal leukopoietic elements, with no evidence of transitional forms. It is concluded that in leukemia there occurs a gradual or sudden transformation of all of the bone marrow elements. The picture of isolated foci of cells possessing neoplastic features was ultimately replaced by that of generalized leukemic infiltration. During remission in 1 case the marrow obtained for study by sternal aspiration was completely restored to normal, whereas in the other 2 remissions were only partial. The author believes that the body possesses a defense mechanism against leukemic cell infiltration of which the nature is obscure. The presence of such cells followed by their disappearance in these cases from the blood and marrow suggests the operation of an immunization process. It is believed that transfusion of blood and arsenical therapy may aid in this process. After a critical review of the literature the author concludes that there are no well authenticated cases of cure of leukemia.

Acute leukemia in a man of 73 years is reported by López Fernandez and Bidot Peralta.[339] The destructive cell type is described as a hemocytoblast, constituting 8 per cent of the cells of the peripheral blood, 57 per cent of those of the marrow and 75 per cent of those of the spleen. The same authors[340] report the case of a youth of 18 years with acute hemocytoblastic leukemia in whom ascites, weakness and low grade fever developed. On first observation the blood was essentially normal, but immature leukocytes were found in the ascitic fluid. Later leukemic changes were observed in the peripheral blood.

In a man of 31 years observed by Paniagua[341] the blood picture underwent a transition during a two month period from one of aplastic anemia to one of myeloblastic leukemia. The patient had been exposed to benzene fumes in his work. During the "aplastic" phase of his illness the findings in the marrow were apparently normal, but later they revealed predominance of myeloblasts. Meuwsen[342] reports a case of acute granulocytopenia, anemia and thrombopenia in a man of 32 years who after recovery from pneumonia underwent a remission of his hematologic condition but later acquired acute parotitis and lymphoblastic leukemia. Ellenberg[343] reports the case of a man aged 44 with a clinical and histologic picture of lymphosarcoma who later exhibited the blood picture of myeloblastic leukemia. Necropsy revealed extensive visceral involvement by tissue of chloromatous type.

Involvement of bone with spontaneous fracture in a case of chronic myelogenous leukemia is reported by Meyer and his associates.[344] Kositchek[345] reports the case of a youth of 19 years with monocytic leukemia associated with osteolytic and osteoclastic changes. Monocytic leukemia is reported by Gueft and Rosahn[346] in an infant of 2 months who before the development of the blood picture of leukemia exhibited numerous bluish gray raised tense, firm nodules in the skin of the trunk, extremities and head, with the histologic features of reticulum cell sarcoma. Roentgen therapy produced a temporary remission.

337. Pearson, B.; Stasney, J., and Pizzolato, P.: Gastrointestinal Involvement in Lymphatic Leukemia, Arch. Path. **35**:21 (Jan.) 1943.

338. Moeschlin, S.: Subakute Paramyeloblastenleukämien mit mehrfachen längeren Remissionen, Deutsches Arch. f. klin. Med. **191**:213, 1943.

339. López Fernández, F., and Bidot Peralta, C.: Sobre una observación de leucemia aguda en el viejo, Rev. méd. cubana **54**:186, 1943.

340. López Fernández, F., and Bidot Peralta, C.: Leucemia aguda hemocitoblástica a forma de ascitis hemorrágica, Rev. méd. cubana **54**:560, 1943.

341. Paniagua, G.: Anemia aplastica por el benzol; leucemia mieloblastica, Rev. clín. españ. **7**:341, 1942.

342. Meuwsen, L.: Beitrag zur Kenntnis der myeloischen Insuffizienz, Klin. Wchnschr. **21**:273, 1942.

343. Ellenberg, M.: Myeloblastic Leukemia with Confusing Leukosarcomatous Infiltrations Resembling Neoplasm, J. Mt. Sinai Hosp. **10**:374, 1943.

344. Meyer, L. M.; Friedman, A. B., and Ginsberg, V.: Infiltration of Bone with Spontaneous Fracture in Case of Chronic Myelogenous Leukemia, Arch. Surg. **46**:514 (April) 1943.

345. Kositchek, R.: Monocytic Leukemia Associated with Bone Changes, Ann. Int. Med. **19**:1008, 1943.

346. Gueft, B., and Rosahn, P. D.: Monocytic (Histiocytic) Leukemia in Relation to a Previously Existing Sarcoma of the Skin: Case Report, Am. J. Clin. Path. **13**:516, 1943.

Arneth [347] discusses the diagnosis and causative factors in cases of acute leukemia and states that various types of infection should be considered as possibly involved in the causation of this condition. He mentions, in particular, miliary tuberculosis and streptococcic infections. Schultz [348] discusses the relationship of agranulocytosis and acute leukemia to typhoid infection. Five cases of either typhoid or paratyphoid associated with leukemia are reported, but the author believes that the infection was secondary to lowered body resistance resulting from the presence of leukemia.

Lesions of the gingivae and oral mucosa accompanying monocytic and myelogenous leukemia are described in cases reported by Ziskin and Zegarelli,[349] Stern and Klaif,[350] Beinfield,[351] and Fitzgerald.[352] Renal complications of leukemia are discussed in communications by Merrill and Jackson [353] and Alexander and his associates.[354]

McGoldrick and Lapp [355] reviewed the literature on pregnancy in the presence of leukemia and found 111 reported cases, of which 79 appeared to be well established. They describe a case under their observation, and a similar case is reported by Moloney and his associates.[356]

Spontaneous rupture of the spleen in a case of acute myelogenous leukemia is reported by Rubnitz.[357] The author discusses the possibility of the splenic injury producing the leukemia, but there seems to be little justification for this hypothesis. He states that 7 cases of rupture of the spleen in leukemia have been reported previously.

347. Arneth, J.: Zur Frage der "akuten Leukämie" qualitativen Standpunkte aus Miliartuberkulose als Ursache, Deutsche med. Wchnschr. **68**:841 and 868, 1942.

348. Schultz, W.: Agranulozytose Leukämie oder Typhus? Deutsche med. Wchnschr. **68**:752, 1942.

349. Ziskin, D. E., and Zegarelli, E. V.: Subacute Monocytic Leukemia, Ann. Dent. **2**:59, 1943.

350. Stern, L., and Klaif, J.: The Stomatitis of Acute Myeloblastic Leukemia, Ann. Dent. **1**:196, 1943.

351. Beinfield, H. H.: Lesions of the Mouth in Myeloid Leukemia, Arch. Otolaryng. **38**:69 (July) 1943.

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353. Merrill, D., and Jackson, H., Jr.: The Renal Complications of Leukemia, New England J. Med. **228**:271, 1943.

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355. McGoldrick, J. L., and Lapp, W. A.: Leucemia and Pregnancy: A Case Report and Review of the Literature, Am. J. Obst. & Gynec. **46**:711, 1943.

356. Moloney, W. C.; Hefferman, R. J., and Kasdon, S. C.: Leukemia in Pregnancy with Report of a Case, J. A. M. A. **122**:1170 (Aug. 21) 1943.

357. Rubnitz, A. S.: Spontaneous Rupture of the Spleen Due to Acute Leucemia or Acute Leucemia Due to Trauma to the Spleen . . . Which? Report of a Case and Review of the Literature, J. Lab. & Clin. Med. **28**:972, 1943.

(To Be Continued)

Book Reviews

Segmental Neuralgia in Painful Syndromes. By Bernard Judovich, M.D., and William Bates, M.D., with a foreword by Joseph S. Yaskin, M.D. Price, $5. Pp. 320, with 178 illustrations. Philadelphia: F. A. Davis Company, 1944.

This is an interesting monograph on segmental neuralgia, which the authors carefully differentiate from visceral pain, and which appears to be due to the many factors which irritate roots, ganglions or trunks of the spinal sensory nerves. Although the syndrome of segmental pain and tenderness has no specific origin and may be due to toxins, poor posture, trauma, arthritis and malignant metastases, it may be considered a clinical entity from a therapeutic standpoint.

There can be no argument about the help that repeated injections of procaine give in such instances. Controversial, however, is the use of the pitcher plant distillate or its active principle, the ammonium salts, which according to the authors mainly affect the slowly conducting C fibers and thus abolishes pain and tenderness for many months without producing anesthesia or motor paralysis. Nevertheless their experiences with intraspinal injection of ammonium salts would indicate that unpredictable bowel and bladder disturbances may occur. It is also to be noted that the sympathetic nervous system seems unaffected by the pitcher plant distillate or the ammonium salts, which would throw doubt, as the authors themselves state, on the general validity of the statement that all C fibers are blocked by the ammonium salts.

With the present neurophysiologic methods, there should be no difficulty in proving or disproving the fact that the ammonium ion actually interferes with chemical or electrical transmission of impulses. The data presented in this book are overwhelmingly based on the subjective reports of patients and can only optimistically be called suggestive. Nor is any proof offered that these solutions are not simply local irritants and act by producing hyperemia. This book should interest many but will convince few.

Bacterial Infection, with Special Reference to Dental Practice. By J. L. T. Appleton. Third edition. Price, $7. Pp. 498. Philadelphia: Lea & Febiger, 1944.

This volume, as its title indicates, is mainly a treatise on infection in general and oral infections in particular. Part I contains a few short introductory chapters on the morphology and cultivation of bacteria, asepsis and antisepsis, and two groups of bacteria, the streptococcus-pneumococcus group and the spirochetes, are taken up in some detail. The subject of immunity is well covered. The remainder of the book, parts II and III, is devoted to the discussion of infection, followed by chapters on dental caries, the bacteriology of the dental pulp. Vincent's stomatitis, osteomyelitis, actinomycosis, focal infection and the oral manifestations of certain extraoral infections.

Although this book could hardly be used as a textbook in a first course in bacteriology for dental students unless accompanied by a satisfactory general text or manual, it would be an excellent reference book for advanced students. It would also serve as an invaluable handbook for the dental practitioner, a purpose for which it was evidently primarily intended. The author has done much research and has read widely, and he makes few statements which are unsupported by evidence from some source. When the available data are conflicting and inconclusive, as in the case of Vincent's infection, for example, they are presented without bias. Much progress in dental research is indicated since the author's previous edition, especially in connection with dental caries. This edition has gained in conciseness, being 150 pages shorter than its predecessors.

Artificial Pneumothorax in Pulmonary Tuberculosis. By T. N. Rafferty, M.D. Price, $4. Pp. xv + 192, with index, bibliography and 26 illustrations. New York: Grune and Stratton, 1944.

This is a modest little monograph and of about the right size to fit into one's pocket. Its coming out is especially well timed because all physicians just now are more determined than ever to keep well informed about tuberculosis and its treatment in order to help in combating whatever tendency the disease has shown of late toward regaining its former position as our most important national public health hazard.

The author writes clearly, is thoroughly familiar with his subject, and is well informed in regard to its recent pertinent literature. He describes modern collapse procedures, giving an account of the several measures most commonly employed and their accomplishments. He predicts that extrapleural thoracoplasty will be performed more frequently in the future and that the popularity of artificial pneumothorax will diminish. He believes that ineffective collapse is by necessity almost a futile method and is responsible for most of the failures. He advocates for all patients careful choice of their form of treatment and believes that this can be best decided only after proper observation under hospital conditions for whatever time is necessary.

The book makes good reading and is informative and well arranged. The illustrations are clear and well selected. The bibliography of 195 references has been culled with discrimination.

A Manual of Physical Therapy. By Richard Kovacs, M.D., Professor of Physical Therapy, New York Polyclinic Medical School and Hospital; Attending Physical Therapeutist, Manhattan State, Harlem Valley State, Columbus and West Side Hospitals. Third edition, thoroughly revised. Price, $3.25. Pp. 309, with 118 engravings. Philadelphia: Lea & Febiger, 1944.

This manual, which was formerly published under the title "Physical Therapy for Nurses," is composed of the following divisions: Introduction; Heat and Light; Electricity; Water; Massage and Exercise, and Applied Physical Therapy. Following the second, third, fourth, and fifth divisions are a series of questions on the contents of the respective parts. The book is replete with pictures which illustrate the various procedures described in the text. Although one might not subscribe to every procedure advocated, every physician could read this manual with profit.

Principles and Practice of Tropical Medicine. Part I. By L. Everard Napier, M.D. Price, $8.00. Pp. 522. Calcutta, India: Thacker, Spink and Company, 1943.

Dr. Napier has had a quarter of a century of experience in the tropics, most of it in India. This extensive experience permits him to write with real authority on such topics as malaria, cholera, kala-azar, epidemic plague and the dysenteries, diseases that are common in that country. A feature of the book that will be appreciated by the student is the consecutive presentation of each disease; this is not characteristic of texts on tropical medicine. Another advantageous feature is the bibliography; it is not overloaded, but the citations that are given are well selected and appear to be accurate. While revolutionary ideas are not expressed, most chapters contain evidence of original thought as well as personal experience, so that even persons familiar with the subjects will find the presentation stimulating. The errors that are present are trifling and were overlooked in proofreading. For instance, São Paulo is placed in Argentina on one occasion but on others has been allowed to remain in Brazil. This volume is only the first part of the book, but it includes most of the important tropical diseases. The book is a valuable addition to the literature on tropical medicine, and it is to be hoped that part II will not be long in forthcoming. It is understood that the book will eventually be published in one volume.

News and Comment

Open Meeting of New York Institute of Clinical Oral Pathology.—The first open meeting of the New York Institute of Clinical Oral Pathology, Inc., will be held in Hosack Hall, New York Academy of Medicine, 2 East One Hundred and Third Street, on Monday, October 30, at 8:15 p. m. There will be a symposium on "Fluorine in Dental Public Health," over which Dr. Arthur H. Merritt will preside.

Further information regarding the meeting may be procured from the executive secretary, Mr. G. Roistacher, 101 East Seventy-Ninth Street, New York 21.

Association of Military Surgeons of the United States.—The annual meeting of the Association of Military Surgeons of the United States will be held at the Pennsylvania Hotel, New York, November 2 to 4. In addition to addresses by the Surgeons General of the Army, the Navy and the Public Health Service and by other distinguished guests, there will be formal papers, panel discussions and scientific and technical exhibits on the latest advances in military medicine.

Symposium at Louisiana State University.—A symposium on the heart and the circulation will be held at the Louisiana State University School of Medicine, 1542 Tulane Avenue, New Orleans 13, on Oct. 25, 26 and 27, 1944, from 9:30 a. m. to 5:00 p. m. each day. Those who are interested are invited to attend. No fee is charged. The visiting participants are Dr. Maurice Visscher, University of Minnesota, who will discuss cardiac efficiency and metabolism; Dr. Isaac Starr, University of Pennsylvania, who will report on the ballistocardiograph, and Dr. Frank N. Wilson, University of Michigan, whose subject will be electrocardiography. Other speakers are from Tulane University and Louisiana State University.